PHD

Atom Economical and Environmentally Benign Metal Catalysed Synthesis

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Atom-Economical and Environmentally Benign Metal Catalysed Synthesis

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Contents

0.1 Acknowledgements

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Finally I would like to acknowledge the support and assistance from my parents and the rest of my family, I could not have dealt with the last three years anywhere near as easily if it hadn't been for your continual help and care!

0.2 Abbreviations

Å Ångstrom

Ac Acyl

Ar Aryl

BEMP 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine

bipy Bipyridyl

BHT 2,6-*tert*-Butoxide-4-hydroxytoluene

Bn Benzyl

°C Degrees centigrade

CDI Carbodiimide

cod Cyclooctadiene

conv. Conversion

Cp Cyclopentadiene

Cp* Pentamethylcyclopentadiene

cy Cyclohexyl

DBN 1,5-Diazabicyclo[4.3.0]non-5-ene

DBU 1,8-Diazabicyclo[5.4.0]undec-7-ene

DFT Density functional theory

DMAB Dimethylamine borane

DMAP 4-Dimethylaminopyridine

DMF Dimethylformamide

DMSO Dimethyl sulfoxide

DPEN Diphenylethylenediamine

DPEPhos Bis(2-diphenylphoshinophenyl)ether

ee. Enantiomeric excess

equiv. Equivalents

Et Ethyl

FLP Frustrated Lewis pair

FT-IR Fourier transform infra-red spectroscopy

g Grams

h Hours

HOAt 1-Hydroxy-7-azabenzotriazole

HPLC High performance liquid chromatography

Hz Hertz

$^{\mathbf{i}}$**Pr** *Iso*propyl

LUMO Lowest unoccupied molecular orbital

M Molar

m *meta*

Me Methyl

Mes Mesityl

MHz Megahertz

min. Minutes

mL Millilitres

mmol Millimoles

MS Molecular sieves

NHC *N*-Heterocyclic carbene

NMR Nuclear magnetic resonance

o *ortho*

p *para*

Ph Phenyl

ppm Parts per million

r.t. Room temperature

TBD 1,5,7-triazabicyclo[4.4.0]dec-5-ene

^{t}Bu *tert*Butyl

TEM Transmission electron microscopy

terpy Terpyridine

THP Tetrahydropyran

Tf Triflate

TLC Thin layer chromatography

TMEDA Tetramethylethylenediamine

TMS Trimethylsilyl

TON/TOF Turn over number/frequency

UV Ultraviolet

0.3 Abstract

Chapter I entails an introduction into the synthesis of amide bonds with particular focus on catalytic methodologies. Discussion is then given to the development of a zirconium catalysed aminolysis methodology with emphasis on the importance of a thiocyanate additive.

Chapter II explores the current literature in the field of metal catalysed acylations with emphasis on the role of acid anhydrides as acylating agents. The results section within describes the application of magnesium iodide as a mild catalyst for anhydride activation with investigations into the mode of activation described.

Chapter III initially details the current applications of amine boranes and the recent literature describing their catalytic dehydrocoupling. This is followed by an account of the use of a ruthenium catalyst to reductively couple nitro-aromatics with nitrile species. Following this is a description of the novel, copper catalysed, reduction of a range of organic functional groups. Mechanistic studies determine the catalytic mode of activation.

Chapter IV is an experimental chapter containing the spectroscopic data for the isolated compounds.

Chapter V summarises the conclusions drawn from the research.

Chapter 1

Aminolysis of Esters

1.1 Introduction

The amide group is one of the most prevalent functionalities in both Nature, such as in proteins, as well as in industrial applications. One of the reasons that it has become so ubiquitous is due to the inherent strength of the carbon-nitrogen bond; this is caused by the donation of electrons from the nitrogen into the π*-antibonding orbital of the carbon-oxygen double bond. This dissociation of the electrons between the three atoms means the carbonyl is much less susceptible to nucleophilic attack and is more robust to potential cleavage by hydrolysis.

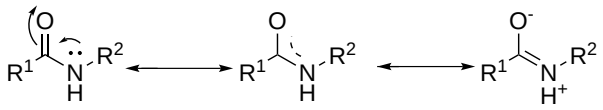


Figure 1.1: Resonance forms of an amide bond

Some of the key industrial uses of amides are in the synthesis and production of drug molecules or agrochemicals with the formation of an amide bond by *N*-acylation being utilised in almost two thirds of the top 128 drug candidates.[1] Of three top pharmaceutical companies surveyed however, there was very little use of catalysis for these bond formations with 44% involving the use of stoichiometric thionyl chloride to form an acid chloride because the by-products; SO_2 and HCl, are easily removed. Approximately a third of the industrial amide formation reactions are carried out with the use of coupling reagents such as CDI which have very poor atom economies.[2] Examples of some of the pharmaceuticals and agrochemicals formed by these methods are shown in Fig. 1.2. Because of the intrinsic disadvantages to the formation of amides through these methods, a survey of pharmaceutical companies picked amide bond formation avoiding poorly atom

efficient methods as the top research area for which new reagents are wanted. This suggests that there is a strong need for alternative, environmentally benign methods for producing amides from readily available starting materials without the production of large quantities of waste.[2]

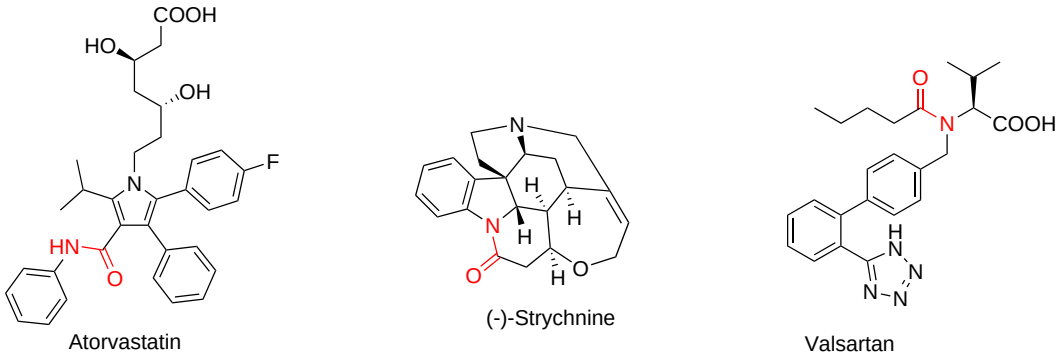


Figure 1.2: Non-catalytically produced amides in industry

1.2 Methods of Amide Bond Formation

1.2.1 Non-catalytic methods.

1.2.1.1 Carboxylic acid activation.

The vast majority of amides are formed from activation of a carboxylic acid to form a more reactive species. This can in turn be attacked by an amine nucleophile to render the desired amide product. As mentioned in the introduction one of the most widely used methods is *via* the Schotten-Baumann reaction Fig. 1.3, whereby the carboxylic acid is reacted to form the more electrophilic acid halide, commonly by the addition of thionyl chloride to give the acid chloride.[3]

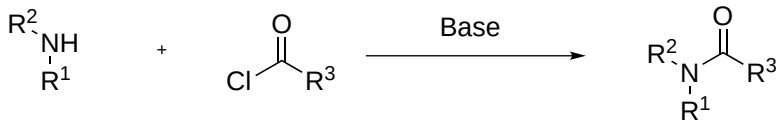


Figure 1.3: Schotten-Baumann reaction

The incoming amine can react more rapidly with this activated substrate, producing the desired amide as well as one equivalent of HCl which frequently requires neutralisa-

tion by one equivalent of base to avoid retardation of the reaction *via* amine protonation. Generation of the acid chloride can be conducted by the use of the thionyl chloride as mentioned or alternatively by the addition of oxalyl chloride with a catalytic amount of DMF, which can be preferential due to the less hazardous by-products formed. These reactions can be expediated with the addition of catalytic DMAP or pyridine and in some cases where the reactions are run in pyridine it is thought that it might proceed *via* the formation of an acyl pyridinium salt.[4]

1.2.1.2 Coupling reagents.

The next most common method for activating the carboxylic acid towards nucleophilic attack is by the addition of coupling reagents such as carbodiimides.[3] In a similar fashion to acid chlorides these compounds activate the carboxylate group to form an *O*-acylurea intermediate that is far more electrophilic and this intermediate can undergo one of four main methods of reaction. The primary route is the attack of the nucleophilic amine to give the expected amide, Route 1, Fig. 1.4. Alternatively however the now activated carboxylate group can undergo attack by another deprotonated carboxylate to generate an acid anhydride, Route 2, Fig. 1.4, which if electrophilic enough to undergo nucleophilic attack, regenerates the carboxylic acid whilst forming the amide. The final possible reactions for the *O*-acylisourea to undergo are either the undesired rearrangement to generate the *N*-acyl urea as in Route 5, Fig. 1.4, or the cyclization to form an oxazolone which can lead to the racemization of enantiomerically pure substrates, Route 3, Fig. 1.4.[4]

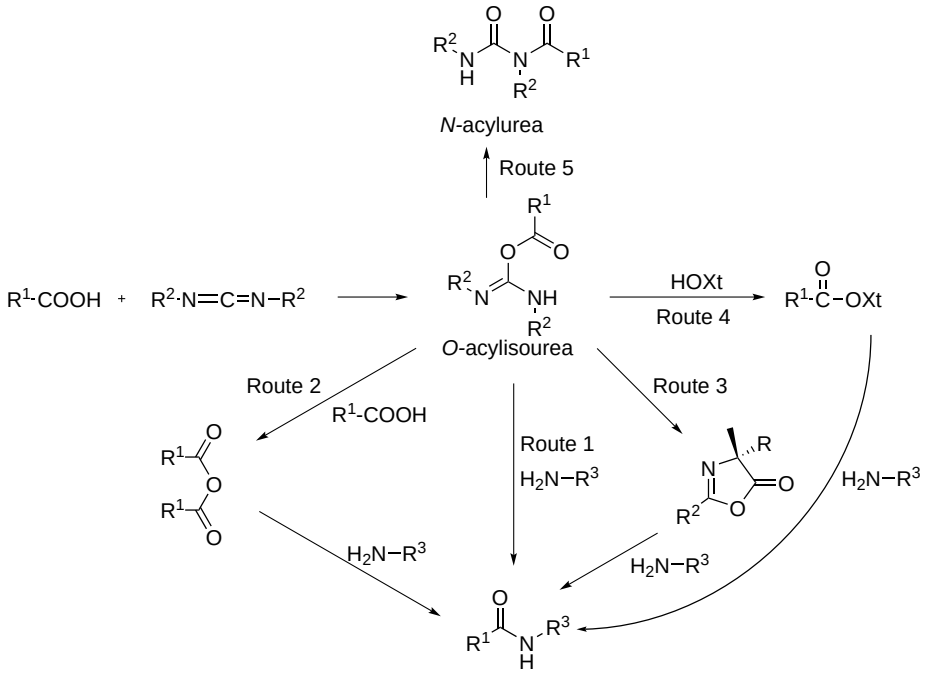


Figure 1.4: Pathways for amide formation with CDI

An example of carbodiimides being used in industry is the application of CDI (carbonyldiimidazole) in the production of Sildenafil citrate by Pfizer where it is used to couple an amino-pyrazole-amide with a benzoic acid to yield an intermediate that could undergo cyclization as in Fig. 1.5. The reason that CDI was used in this case, over the alternatives, was because it allowed for the combination of three different processes (hydrogenation, activation and acylation) to provide a clean, robust route to the desired product, compensating for the expense of the reagent.[5]

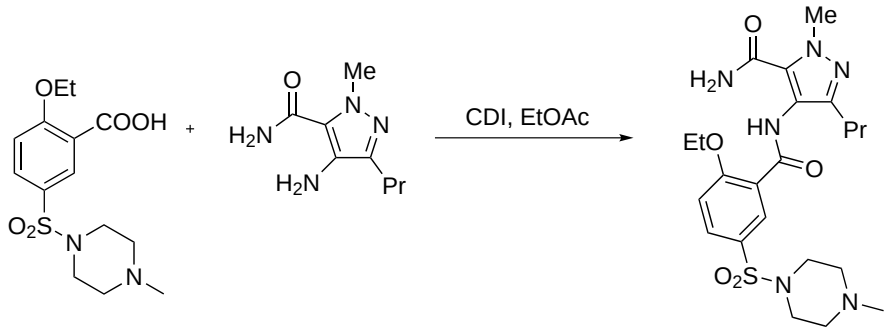


Figure 1.5: Commercial route to Sildenafil citrate

Many advances have been made to the process of using carbodiimides as coupling

reagents; an example of this is the addition of additives such as *N*-hydroxy derivatives (HOXt), Route 4, Fig. 1.4. These aid the reaction by two main mechanisms; firstly they are able to protonate the *O*-acylisourea hindering formation of the undesired *N*-acylurea as well as diminishing the production of the oxazolone which, although a possible intermediate to the desired amide, does pose problems when retention of chirality is required. The second benefit arises from the increased stability of the leaving group due to the nitrogen atoms stabilising the electron density. A particularly efficient additive is 7-HOAt which, due to the nitrogen atom in the 7-position on the ring, is able to act as a neighbouring-group by directing and activating the incoming amine Fig. 1.6.[4]

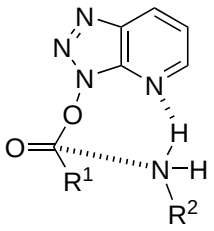


Figure 1.6: Neighbouring group interaction of 7-HOAt

1.2.1.3 Thermal amidation of carboxylic acids.

The final method of non-catalytic amide bond formation discussed herein is the formation of an amide product by thermal amidation. Whilst the direct coupling of an amine to an unactivated acid has been known since 1858 there are some significant drawbacks to this atom economical method.[6] The primary failing is the interaction of the protic acid with the basic incoming amine. This leads to the production of the carboxylate salt that is no longer as susceptible to nucleophilic attack. One of the earliest methods to circumvent this issue was the use of forcing conditions, in particular very high temperatures such as done by Reid and Mitchell in 1931. In this example the primary amides of simple aliphatic acids were formed in good yields by passing ammonia gas through the solution at temperatures in excess of 150 °C.[7] The high temperatures also benefit the reaction by removing some of the water, produced by the condensation of an acid with an amine, shifting the point of equilibrium, potentially favouring formation of the amide. Fig. 1.7. Noticeable hindrances to these methods gaining wider practical use however was that the substrate scopes were generally limited to unfunctionalised aliphatic acids and also the high temperatures needed could result in dehydration of the primary amide to the corresponding nitrile.

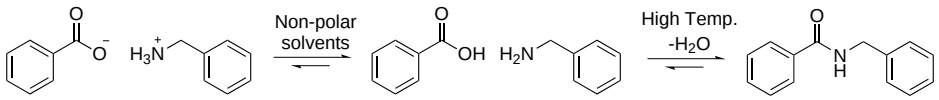


Figure 1.7: Acid-amine equilibrium

An alternative method to avoid the formation of the ammonium carboxylate is to use various salts of the starting materials. An early example of this is in the 1902 paper by Dunlap where it is shown that the use of sodium carboxylate salts when added to the hydrochloric salt of the amine gave the corresponding amide along with stoichiometric sodium chloride. The yields however were mediocre to poor and the reaction required elevated temperatures and extended reaction times.[8] There was relatively little literature in the field following these publications for quite a while, primarily due to the versatility of the activating methods mentioned above, until a paper by Cossy in 1989. This described the use of activated molecular sieves to remove the water produced in the reaction and was shown to produce high yields of primarily aliphatic secondary amides although some highly nucleophilic secondary amines were also shown to couple.[9] More recently Gooβen *et al.* have shown that the addition of molecular sieves is not always necessary although it does stop the production of high pressures when used in a closed system. A wide variety of amides was synthesised by this method with good functional group tolerances in mostly high yields, the exception being for secondary anilines.[10]

Attempts to lower the temperature required for amide formation have been made by many groups; one noticeable report is the solvent-free microwave induced coupling of acids with amides. This showed higher reactivity under microwave conditions even in the presence of mechanical stirring to remove macroscopic hotspots, suggesting that specific non-thermal microwave effects were seen. Of particular note was the use of non-stoichiometric amounts of the substrates, for example increasing the ratio of benzylamine to benzoic acid from 1:1 to 1.5:1 increased the yield under microwave conditions from 10 to 80%. With the yield dropping upon further increase of benzylamine and a similar pattern seen with an excess of benzoic acid relative to the benzylamine, it was postulated that the reaction was being promoted by acid catalysis. This effect can be caused by a proton from either the amine or acid binding to the carbonyl, reducing the electron density, enhancing its electrophilic nature promoting catalysis by this method. Fig. 1.8.[11]

Figure 1.8: Protic carbonyl activation

Recently work within our own group has focussed on trying to lower the reaction temperatures further, without relying on the microwave effect increasing the nucleophilicity of the incoming nitrogen nucleophile. It was noticed that when trying to couple 3-phenylpropanoic acid with 4-methyl benzylamine in the presence of hydroxylamine hydrochloride the uncatalysed reaction was surprisingly high, 18% after 4 h compared with 9% for the catalysed version when run in toluene. It was postulated that the use of toluene, which as a non-polar solvent, was hindering the formation of the charged species which retard coupling, Fig. 1.7. A thorough solvent, temperature and concentration screen showed that 2M reactions run in toluene proceeded well for a very wide range of both acids and amines and coupled in mostly excellent yields.[12]

1.2.2 Non-metal catalysed amide bond formation

1.2.2.1 Boron

Boron reagents were first reported to promote the formation of amide bonds in 1970 where Nelson *et al.* showed that trisalkyl-, trisalkoxy-, dialkoxy- and chlorodialkoxyboranes were all capable of coupling acids with amines. It was postulated that the reaction proceeded *via* an acyloxyalkoxyborane intermediate, which has an activated carbonyl for nucleophilic attack, without proceeding through an acid anhydride intermediate. Trimethoxyborane was noted to be particularly useful considering its high efficacy and low cost, these reactions however required heating (65 °C) which, although generally considered relatively mild, does discount this method for the purpose of amide bond formation in most peptide synthesis due to denaturing of the substrates. A particularly early and important use of a boron reagent as a catalyst was the use of 3,4,5-trifluorobenzeneboronic acid which was shown to couple 4-phenylbutanoic acid with 3,5-dimethylpiperidine in good yields at 5 mol% catalyst loading. It is thought that the electron withdrawing nature of the aryl ring stops the catalyst from forming inactive species after the initial amidation of the *in situ* formed acyloxyboron species, as well as contributing to the thermal and air stability. The proposed mechanism initiates with the

breaking up of a cyclic trimeric boroxine species by addition of a carboxylic acid. This produces the monomeric acylalkoxyborane upon further hydrolysis. This species is then attacked by the incoming amine, forming the amide whilst regenerating an aryl-boronic acid that can condense to form the initial trimer, Fig. 1.9.

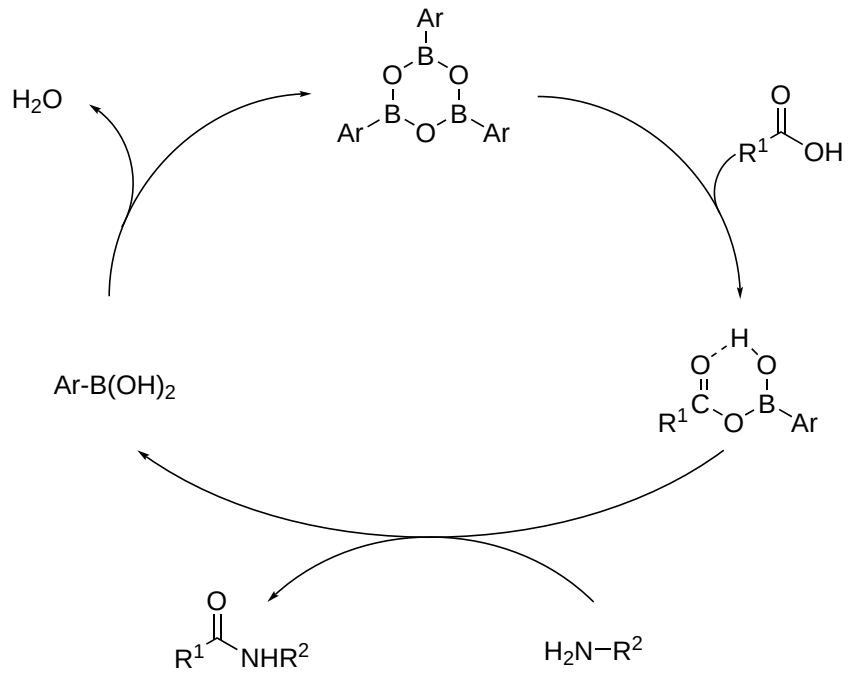


Figure 1.9: 3,4,5-Fluorobenzeneboronic acid catalysed amidation

Importantly, although this method was shown to work with low catalyst loadings, it still required the use of molecular sieves in a Soxhlet capsule to absorb the water produced by the reaction. It was also shown to work for the production of esters from the corresponding alcohols however a caveat is that it requires the use of heavy alcohols, butylalcohol and above, to produce reasonable yields.[13] A more recent paper published by Whiting *et al.* shows good agreement with the suggestion that electron withdrawing substituents (p-F_3C-) on an aromatic ring promote the efficiency of arylboronic acid catalysts, whilst electron donating (MeO-) diminish the efficacy of the catalyst. This paper also notes the importance of removal of water in the reaction as this changes both the final conversions produced as well as the rate of the reaction. The optimised catalyst and reaction conditions found are given in Fig. 1.10.[14] The scope of this catalyst was shown by Yamamoto *et al.* to enable the direct catalytic coupling of acids with ureas to form N-acyl ureas. The products were then shown in the paper to undergo dehydration to nitriles when a perrhenic acid catalyst was introduced; this suggests that this

one pot reaction could allow for the use of urea as a synthetic equivalent of ammonia.[15]

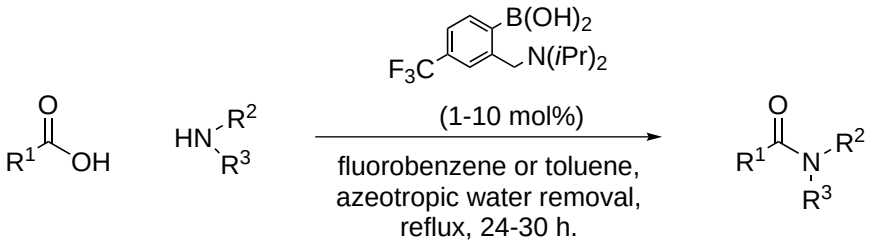


Figure 1.10: Optimised conditions for the arylboronic acid catalysed direct amide formation

Shortly after, the same group expanded on their work to show that reasonable levels of kinetic resolution could be achieved by using chiral boronic acids as the catalysts with only mildly activated acids. The reaction between α-methylbenzylamine and benzoic acid was shown to produce the desired amide in 21% conversion after 48 h with an enantiomeric excess of 41% when using (*p*S)-2-(2-boronoferrocenyl)-*N*-*n*-butylbenzimidazole as the catalyst, Fig. 1.11.[16]

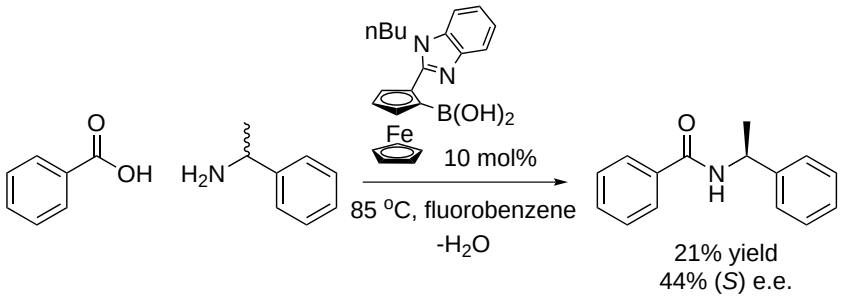


Figure 1.11: Chiral boron catalysed kinetic resolution of amines to form amides

Recently, research in the area of arylboronic acids as catalysts for the direct coupling of acids with amines has focused on the use of *ortho*-iodoboronic acid catalysts. It was found that the introduction of a halogen (Br or I) at the *ortho* position significantly increased the reactivity of the catalyst and in contrast to similar non-*ortho*-halogenated arylboronic catalysts the authors saw a decrease in catalyst efficiency upon the addition of electron poor substituents to the aromatic ring. Electron donating substituents were therefore investigated and it was shown that methoxy- groups, *para*- to the boronic acid had very little effect on overall conversion but when placed *para* to the iodo group there was a dramatic increase in conversion. The authors believe that the electron density on the iodide and its relative proximity to the boronic acid are the overriding factors

affecting catalyst reactivity in these cases and that the positioning of the MeO- group *para* to the boronic acid will decrease the required acidity whilst placing such a group *para* to the iodide increases the desired electron density on this atom.[17] In order to increase the industrial applicability of this method, the same group devised a solid supported *ortho*-iodoarylboronic acid catalyst which produced amides in moderate to good yields at room temperature although molecular sieves were still required to remove the water produced.[18]

One final recent development in the boron catalysed direct amidation of carboxylic acids was reported by Sheppard *et al.* where a simple fluorous alkoxyboron reagent [$B(OCH_2CF_3)_3$] is used for the coupling of a very wide range of acids and amides in good yields. As well as the ability to couple protected amino acids with amines without the loss of stereochemistry at the α-position and to also perform intermolecular lactam formation, a particular benefit of this method is the simplicity of purification. The use of three solid phase scavenging resins (Amberlyst acid and base scavenger and Amberlite boron scavenger) followed by drying over $MgSO_4$, filtration and removal of the solvent was all that was required to isolate the desired product without the need for washing or chromatography.[19]

1.2.2.2 *N*-Heterocyclic carbenes.

An alternative to the use of boron reagents for catalytic amide bond formation focusses on another noteworthy metal free method. NHCs (*N*-heterocyclic carbenes) are commonly considered as functional ligands for metals but they have also been shown to be able to act independently to catalyse the acylation of amines by aldehydes with a reactive bond in the α-position as the acyl donor. Back-to-back papers by Vora *et al.* [20] and Bode *et al.*[21] in 2007 showed high conversions and yields for acylation although in both cases either an additive or a co-catalyst was required for the coupling. In the paper by Bode *et al.* a mesityl protected triazolium carbene was used, in conjunction with a super-stoichiometric quantity of imidazole, to generate the activated carbonyl that could be attacked by the amine. The use of catalytic imidazole led to acceptable yields of amide but did not fully suppress the competing imine formation reaction. The role of the imidazole was believed to be acting as a co-catalyst with the NHC and forming the electrophilic acyl imidazole Fig. 1.12. A later expansion of this work by the same group revealed that α-hydroxyenones can also act as the acyl donor by a similar mechanism with loss of acetone and enolisation of the carbon-carbon double bond.[22]

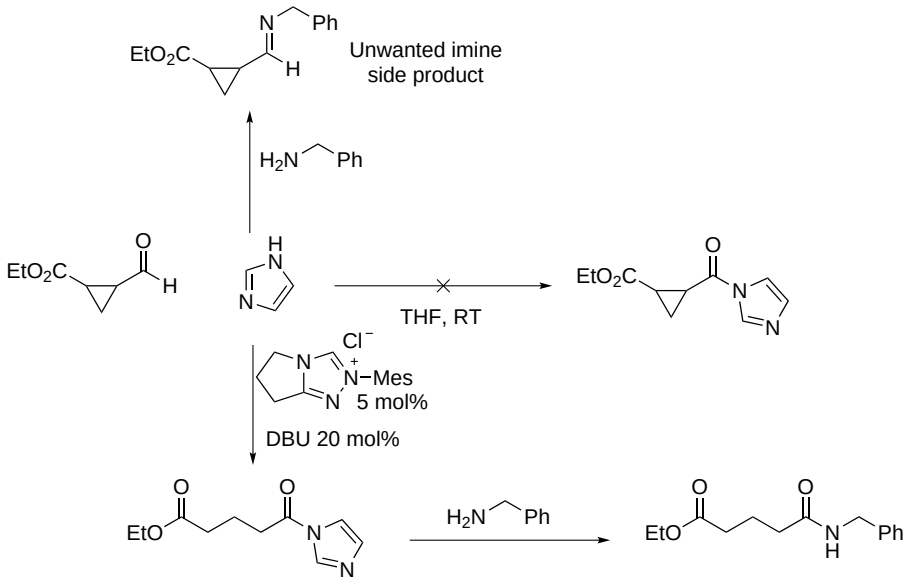


Figure 1.12: NHC catalysed mechanism proposed by Bode *et al.*

Vora *et al.* used a similar catalyst (the tetrafluoroborate salt of the pentafluorobenzene protected triazole) to couple α-activated aldehydes with amines utilising the co-catalyst, HOAt, which has previously been shown to enhance the activity of CDI coupling agents. Commonly used substrates given as examples in the paper are α-halogens (Cl or Br) and α-epoxides or aziridines although the use of α,β-unsaturated aldehydes also show good propensity towards coupling. The HOAt co-catalyst acts in a similar way to before by which it binds to the carbonyl to form an acyl donor species. In this situation however it does so by displacing the NHC and reforming the active catalyst. Fig. 1.13. Whilst this method shows good reactivity towards even anilinic nucleophiles one of the drawbacks of the method is the requirement of an organic base in up to super-stoichiometric amounts. This could be considered an acceptable compromise particularly when considering that when a chiral NHC is used as the catalyst on di-α-halogenated aldehydes there is selective removal of one of the prochiral chlorides in moderate to good enantiomeric excesses.[20]

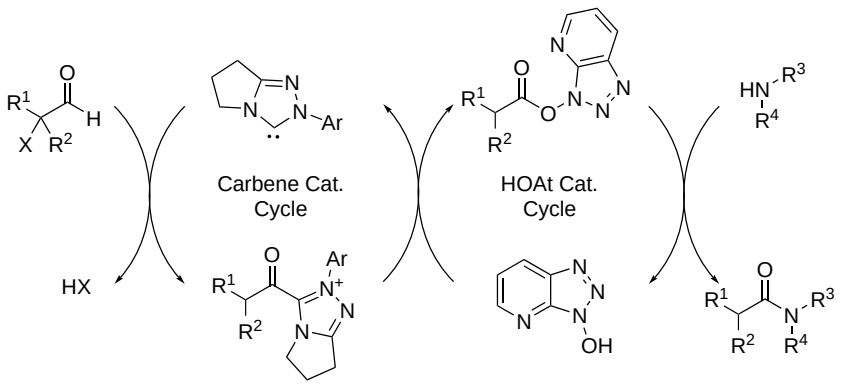


Figure 1.13: Postulated catalytic cycles for the NHC, HOAt co-catalyst system

1.2.2.3 Organo-catalysed amide formation.

In the past few years there have been a few papers reporting organo catalysts for acyl transfer being used to form secondary and tertiary amides in good yields. One of the first examples of this was reported in a paper by Mioskowski and co-workers in 2007 where they made use of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), under solvent free conditions, to produce amides by the aminolysis of alkyl and aromatic esters. The conditions were optimised to show that the reaction was favourable in less polar solvents and could even be conducted over 12 h at room temperature in solvent free conditions, if 30 mol% of the TBD catalyst was used, whilst maintaining the stereochemistry of incoming nucleophiles. The authors demonstrated the ability to couple; cyclic, acyclic, aromatic as well as aliphatic amines with a variety of esters in good to excellent yields. The postulated mechanism is shown in Fig. 1.14, and suggests the production of the TBD amide before attack by the incoming amine regenerates the catalyst.[23]

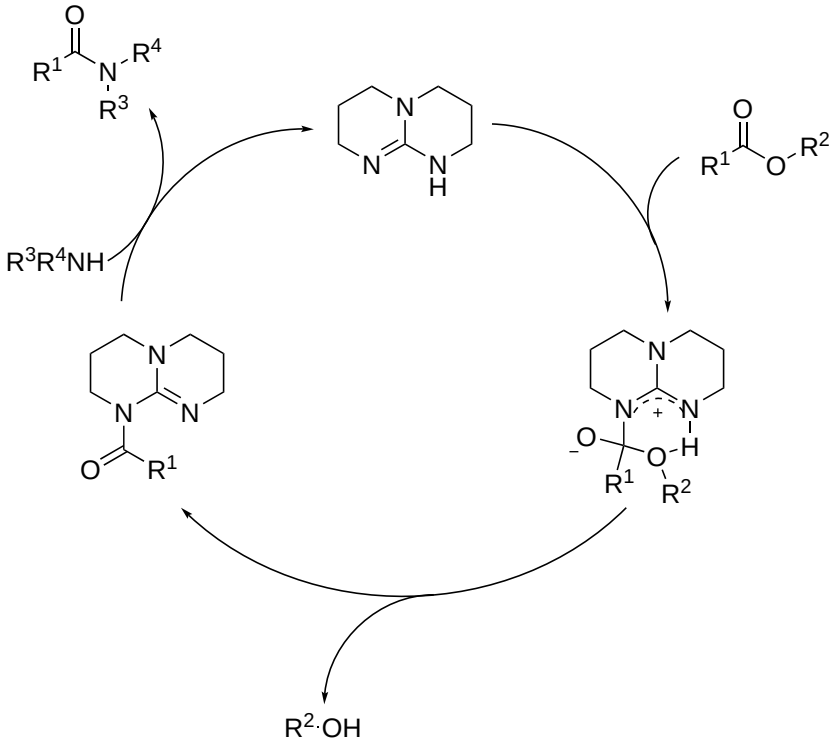


Figure 1.14: TBD catalysed acylations

Building on this work, the group of Birman looked at the use of anionic nucleophiles to catalyse the aminolysis of esters since it was believed that they might show greater nucleophilicity compared with the TBD catalyst. A screen of protic nucleophiles in the presence of DBU showed high activity for a series of azoles, in particular 1,2,4-triazole, whilst removal of the DBN showed little catalytic activity, promoting the hypothesis of an anionic mode of catalysis. It was noted by the authors that the reaction rate dropped off significantly at higher conversions. This was attributed to build up of the alkoxide anion and so the experiment was run with isopropenyl acetate which, due to the ability of the enolate formed to tautomerise to acetone, did not show the same detrimental effects at high conversions. The mechanism for this is given in Fig. 1.15 and allowed for high conversions using only 5 mol% catalyst with 5 mol% DBU.[24] A publication later that year showed the benefits of incorporating the attributes of both of these methodologies when Waymouth and colleagues reported the acylation of simple amines catalysed by TBD using vinylacetate within 6 min at room temperature. Whilst this reaction does occur in the absence of catalyst it is markedly slower. They do however report the required use of four equivalents of amine which will not always be practical.[25]

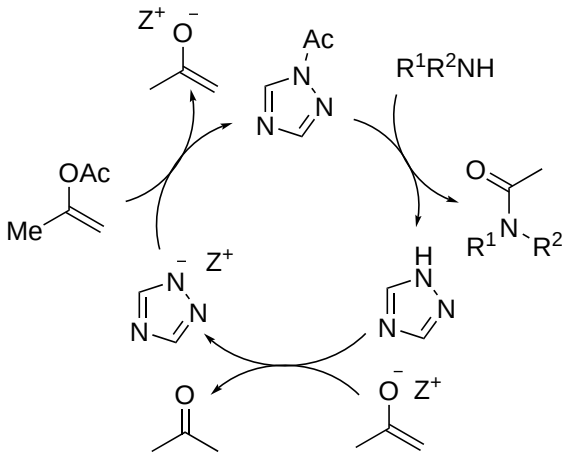


Figure 1.15: 1,2,4-Triazole catalysed aminolysis of isopropenyl acetate

The last example of non-metal catalysed acylations of amines involves the use of an organic base. The authors having noted the use of K(O^{t}Bu) for the aminolysis of esters tried to find an improved alternative. From a series of base and solvent screens they identified that employing 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) in acetonitrile gave the best results. As a result of high throughput, design of experiment techniques the authors reported the optimised conditions for *N*-acylating amino alcohols as; 10 mol% catalyst loadings at room temperature in a 2M concentration for 15 hours. A wide range of amides was isolated in poor to excellent yields at room temperature, the authors did report considerably higher yields for the challenging substrates if the temperature was increased to 40 °C.[26]

1.2.3 Metal catalysed amide bond formation.

1.2.3.1 Introduction.

There are many methods for the metal catalysed formation of amides from a wide range of starting materials using a diverse number of metal catalysts. This section focusses on their synthesis from some of the more common synthetic feedstocks and seeks to prioritise the salient and current literature in each field. A range of different mechanisms will be accounted for with emphasis on the catalytic formation of amides from the amidation of esters.

1.2.3.2 Amides from alcohols.

One of the most appealing reasons for using alcohols as a starting material for the

formation of amides is that the overall reaction can be very atom efficient with just molecular dihydrogen produced as a by-product in the ideal reaction. Much work has been done in the area both by our own group and others. The pioneering paper in the field was a report by Milstein *et al.* in 2007 whereby an elegant catalytic ruthenium pincer complex was reported with a method of action that had previously only been reported for the acylation of alcohols with loss of dihydrogen.[27] The proposed mechanism for this reaction is given in Fig. 1.16 and shows the integral role of the dearomatisation/rearomatisation of the pyridine ring in the catalytic cycle to be able to release the molecular dihydrogen. Experiments were conducted in order to determine whether the reaction proceeded through the originally expected route of; oxidation of one molecule of alcohol to an aldehyde along with the oxidative coupling with another alcohol molecule to form an ester which could undergo aminolysis to product the amide. It was seen however that exposing the ester, the expected intermediate, to the reaction conditions in the presence of amine, it did not produce the amide in agreement with the hypothesised mechanism leading to the revised scheme shown. Whilst this methodology described a very atom efficient synthesis of secondary amides the system was not robust enough to catalyse the formation of tertiary amides from an incoming secondary amine and there were only moderate conversions seen for non-nucleophilic amines such as aniline.

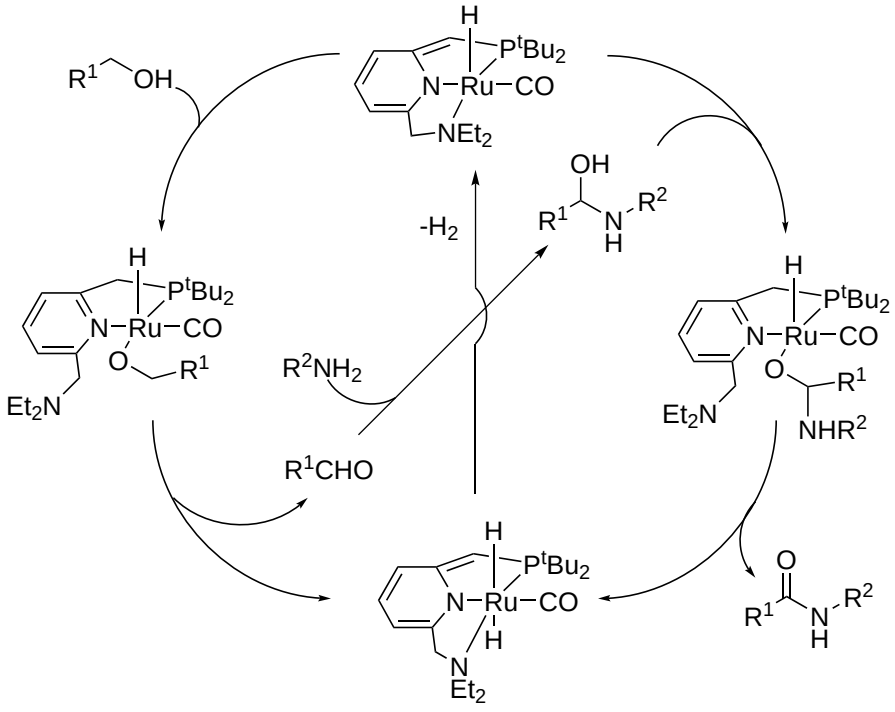


Figure 1.16: Catalytic cycle suggested for Milstein's catalyst

The following year saw Madsen and co-workers publish a report also using a ruthenium based catalyst, for the conversion of alcohols and amines into amides. In addition to Milstein's report this catalytic system also recycles by the effusion of molecular hydrogen. In this case a $Ru(cod)Cl_2$ precatalyst was investigated alongside a range of phosphine ligands and NHCs where it was found that mono-phosphines with a large cone angle were preferable for the reaction in conjunction with saturated NHCs with aliphatic *N*-substituents. The standardised reaction conditions with the designated optimal NHC catalyst are shown in Fig. 1.17, and were demonstrated to work for a limited range of alcohols and amines. It was found by the authors that much higher temperatures were required for anilinic nucleophiles and that sterically hindered substrates only showed low yields.[28]

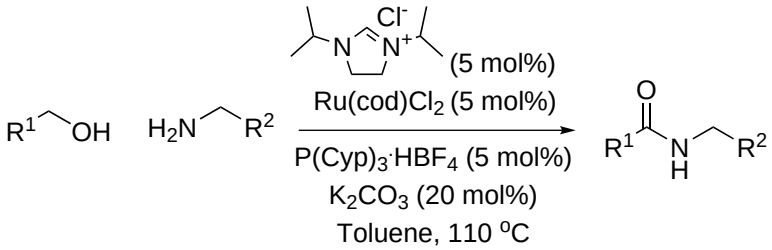


Figure 1.17: Optimised conditions for Ru NHC catalysed oxidative amidation of alcohols

Pioneering work by Murahashi was done using a dihydridotetrakis (triphenylphosphine) ruthenium(II) catalyst and benzylacetone as an acceptor substrate for hydrogen in the condensation of amino alcohols to produce lactams containing 4 or 5 carbons chain length. The reaction scope was expanded to intermolecular reactions whereby nucleophilic, cyclic secondary amines were also shown to couple with a small range of benzaldehydes.[29] This was followed up by work published from within the Williams group which in contrast to the two earlier examples uses a sacrificial hydrogen acceptor, both to oxidise the initial alcohol and to oxidise selectively the hemiaminal formed as an intermediate in the reaction, regenerating the active catalyst. One of the particular benefits of this approach is that it was at the time the the only literature preparation that utilised a commercially available ruthenium catalyst to produce secondary amides and that cheap and readily available feedstocks such as acetone, could be used as the sacrificial hydrogen acceptor although it was noted that 3-methyl-2-butanone gave higher selectivity for amide over amine in some cases. The proposed catalytic cycle is shown in Fig. 1.18, and of note is that the hemiacetal more readily undergoes oxidation rather than the elimination of water to form the imine. Interestingly there was also no reported reaction between the amine and the sacrificial hydrogen acceptor ketone which was

accounted for by the reversibility of the reaction and the instability of the ketimine.[30]

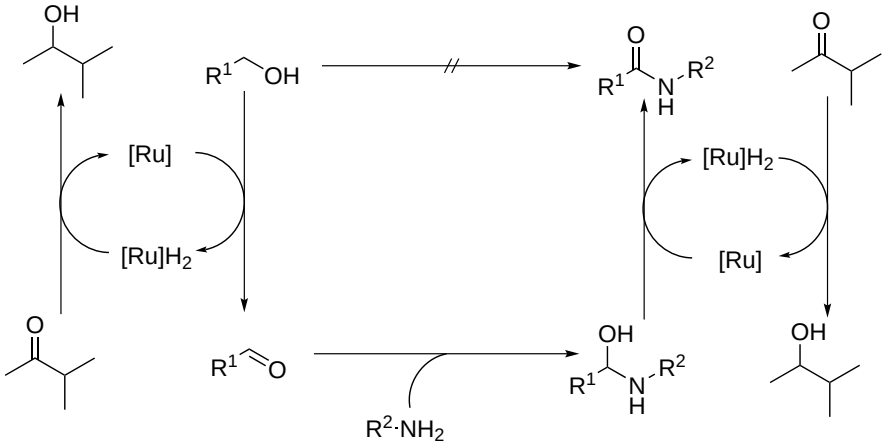


Figure 1.18: Amide formation by ruthenium catalysed transfer hydrogenation

Whilst there are many variations on these themes in the current literature, the three examples give a good basis to the different main modes of activation of alcohols towards amidation and the mechanisms of hydrogen release or transfer. One point of note in the contemporary literature is the publication, again by Milstein and co-workers, which shows how the catalysts have developed further and now have the ability to couple secondary amines to alcohols to give the corresponding tertiary amides, overcoming some of the previous limitations. Whilst the mechanistic principle is believed to be the same as described in Fig. 1.16, the catalyst has been modified to a PNN-bipyridyl ruthenium complex which can be utilised in very low catalyst loadings (0.2-0.4 mol%) from either the active dearomatised catalyst or from the aromatised precatalyst with the addition of catalytic amounts of KO^tBu.[31]

1.2.3.3 Amides from aldehydes

The direct amidation of aldehydes with amines and an oxidizing agent can be conducted without the need of a catalyst as shown by Wolf *et al.* in very good yields.[32] A key disadvantage of this method is the highly reactive *tert*-butyl hydrogen peroxide reagent required to achieve the high yields. The paper also reports the production of only tertiary amides from both cyclic and acyclic amines as well as from amine borane starting materials. In order to gain greater acceptance for industrial purposes lower temperatures and preferably shorter reaction times would be required, compared with the 24 h, 80 °C standard conditions reported by Wolf.

A catalytic method for aldehyde amidation was reported by Marks and Seo with the

benefit of reacting to completion at room temperature rather than requiring reflux in acetonitrile as was the case for the non-catalysed method.[33] Marks' method uses homoleptic Ln[(N(SiMe$_3$)$_2$]$_3$ lanthanide amido complexes (where by Ln = La, Y or Sm) and has been shown to produce a large range of secondary and tertiary amides in moderate to good yields whilst tolerating a wide variety of functional groups. The diagram below, Fig. 1.19, shows the authors' suggested mechanism for the amidation of aldehydes. Of note in the mechanism is the near instantaneous protonation of the lanthanide amido complex with an incoming amine that sets up the catalytic cycle and the undesired side reaction that can produce the homo-coupled ester product. It was shown in the paper that of the lanthanides investigated, lanthanum was the most efficient followed by samarium then yttrium.Increasing the ratio of either amine or catalyst did not affect the yields particularly, altering the ratio of aldehyde however used had a significant effect. This was attributed by the authors to the aldehyde's dual role as substrate and hydrogen acceptor and was further evidenced by the ability of electron poor aldehydes to produce higher yields than their electron rich counterparts. Interestingly, small conversions of primary amine to secondary amide were seen, although it was thought that the competing reaction of imine formation with the production of water was poisoning the sensitive catalyst stopping this reaction producing high yields.

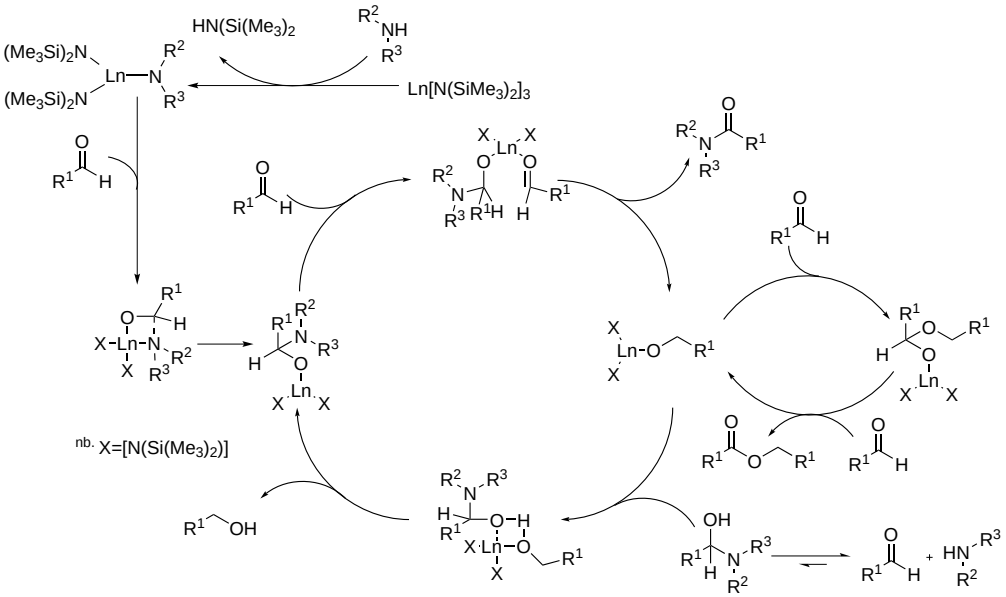


Figure 1.19: Mechanism for lanthanide catalysed amidation of an aldehyde

A similar paper by Beller and co-workers described the use of a cationic rhodium catalyst which was shown to promote the disproportionation of hemiaminals formed by

the addition of a secondary amine to an aldehyde, into the corresponding amide and tertiary amine. The use of *N*-methyl-morpholine-*N*-oxide as a mild stoichiometric oxidant was shown to produce the amide selectively over the amine in very high yields.[34] Yosida *et al.* report an alternative oxidation mechanism that employs stoichiometric arylhalides, in particular bromobenzene, for the formation of morpholine amides of a variety of benzaldehydes. The mechanism for the oxidative amidation is given in Fig. 1.20, and some of the key points to note are the deprotonation of the hemiaminal to give the potassium salt, followed by transmetalation to give the palladium bound species.

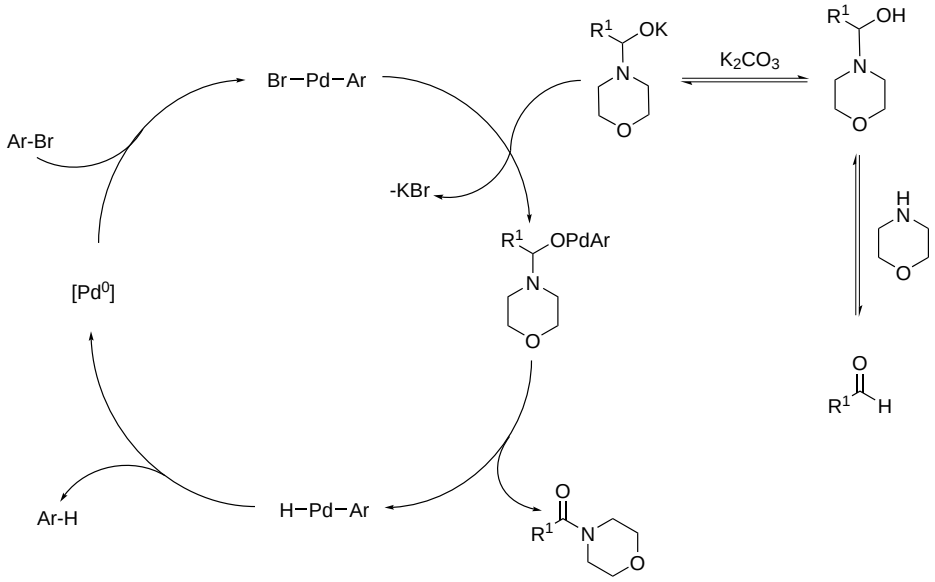


Figure 1.20: Palladium catalysed amidation utilising an aryl-halide oxidant

1.2.3.4 Aminocarbonylation.

Although not explored here in great depth; aminocarbonylation, a process developed initially by Heck *et al.* in 1974, is noteworthy in particular with regards to its similar mechanism to the above reactions of arylhalides seen in Fig. 1.20. In their seminal publication, Heck and co-workers describe the addition of aryl and vinyl halides to primary and secondary amines under one atmosphere of carbon monoxide to form the secondary and tertiary amides in medium to good yields under fairly mild reaction conditions (60-100 °C, 1-10 h).[35] Whilst there has been a considerable amount of interest and related publications in the intervening four decades it is worth mentioning a few of the salient publications. The first by Buchwald in 2007 tackles the relative incompatibility of aryl chlorides in the reaction. These substrates are intrinsically less reactive due to the greater carbon-halide bond strength compared with aryl-bromides,

-iodides or-pseudohalides such as triflates. In the paper Buchwald *et al.* describe how the addition of two equivalents of a basic additive, namely sodium phenoxide, markedly increased the efficiency of the reaction, allowing for lower temperatures to be used to form electron-poor, -neutral or rich variations of tertiary or secondary amides. The role of the phenoxide is shown in Fig. 1.21, which demonstrates its bi-functionality of forming a reactive intermediate ester from the palladium acyl species, then acting as a Brønsted base to catalyse the aminolysis of this ester.[36]

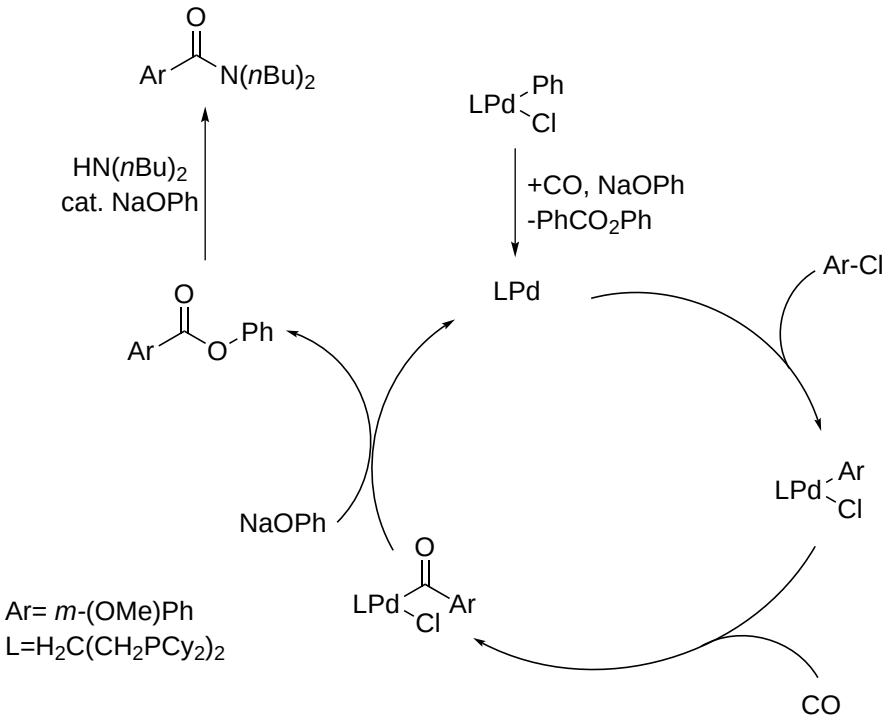


Figure 1.21: NaOPh as an additive to palladium catalysed aminocarbonylation

Other notable publications in the field have been the use of $Mn(CO)_6$ as a solid source of carbon monoxide to avoid the hazards associated with gaseous carbon monoxide. These microwave irradiated reactions were completed very rapidly, albeit at high temperatures and utilising less readily available aryltriflates. Yields in these reactions were noticeably increased with the addition of two equivalents of DMAP and it was proposed by the authors that the reaction might be proceeding through an acylated DMAP intermediate. It was thought the DMAP would be acting as an acyl transfer reagent from the acyl-palladium, formed through CO insertion, to the amine to give the desired amides in noticeably better conversions.[37] At a similar time a publication from Bahanage *et al.* described a preparation for amides by aminocarbonylation in water using the

readily available and inexpensive catalyst $Pd(OAc)_2$ without the need for extraneous ligands. The ability to be able to run the reaction in an environmentally benign solvent such as water and with low catalyst loadings illustrates the feasibility of this method for industrial purposes. The authors proved that a range of electronic effects, on both the aryl iodide and anilinic starting materials, were tolerated as was a considerable amount of steric bulk without seeing a marked reduction on isolated yields.[38]

1.2.3.5 Rearrangement from oximes and ketoximes.

The formation of amides from oximes can be divided into three general reaction types;

- The Beckmann rearrangement of oximes
- The metal catalysed rearrangement of aldoximes into primary amides
- The catalytic acylation of amines with aldoximes

The Beckmann rearrangement was first reported in the 19^{th} century and required a strong acid, with the original Beckmann mixture consisting of acetic acid, hydrogen chloride and acetic anhydride [39] being initially used to instigate the rearrangement. The acid protonates the hydroxyl group converting it into a good leaving group, an alkyl group then migrates on to the nitrogen as the water leaves forming an iminium or nitrilium species depending on whether the starting material was cyclic or acyclic respectively. Water can then recombine with the substrate to yield the amide product after proton transfer. It is worth mentioning that it is generally the group that is *trans*- to the hydroxide of the oxime is the group that migrates as it interacts with the σ^* orbital of the N-O bond as can be seen in Fig. 1.22.

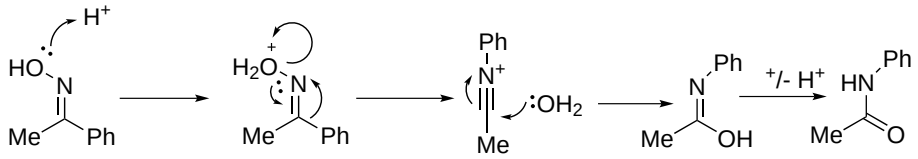


Figure 1.22: Beckmann rearrangement

The second rearrangement mentioned is the metal catalysed rearrangements of aldoximes. A lot of this work focuses on highly expensive metals such as Rh, either on

solid support as $Rh(OH)_x/Al_2O_3$ [40] or with *N*-heterocyclic carbene (NHC) ligands, e.g.. [Rh(cod)(iMES)Cl] [41] as a homogeneous alternative. Both of these methods produce high yielding reactions in relatively short times with high selectivity for the amide product over nitrile side products. The heterogeneous rhodium catalyst of Mizuno *et al.* has the added advantage of being recyclable producing conversions of >99% with respect to the starting aldoxime and a yield of amide of 91% upon reuse.[40] Other metals of lesser cost have been investigated both as super-stoichiometric reagents such as manganese [42] and nickel [43] as well as more recent catalytic rearrangements with non-precious metals rather than ruthenium examples such as Crabtree's $TerpyRu(PPh_3)Cl_2$ catalyst [44] and our own group's $Ru(PPh_3)_3(CO)H_2$ [45] catalyst. Currently some of the most cost efficient processes for amide formation from aldoximes involve the use of $InCl_3$ or $ZnCl_2$.[46] The rearrangement of aldoximes is believed to proceed *via* a nitrile intermediate. This can be seen from conducting the aforementioned $ZnCl_2$ catalysed rearrangement in acetonitrile where acetamide is produced whilst the oxime is converted into a nitrile.[47] Several ^{18}O-labelling studies were conducted to elucidate the mechanism by which the rearrangement of aldoxime to primary amide took place, the purpose of which was to determine the origins of the oxygen atom in the amide product. The result of these reactions suggests that this oxygen atom comes from an oxime molecule rather than through hydrolysis of the nitrile by a water molecule. Crossover reactions show that addition of a labelled oxime to one equivalent of unlabelled oxime under the standard reaction conditions led to scrambling of the ^{18}O label in the amide products. From these results the following mechanism for oxime rearrangement was proposed by the authors, Fig. 1.23.[47]

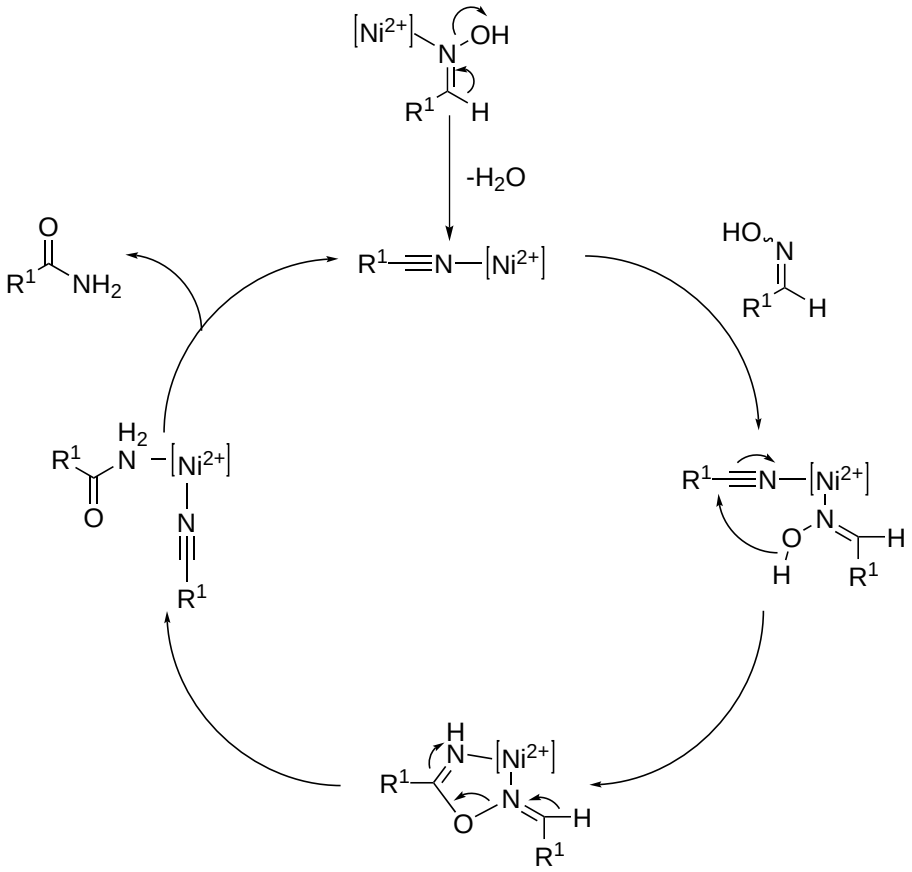


Figure 1.23: Proposed mechanism for the nickel catalysed rearrangement of oximes

The interception of the nitrile intermediate species by an amine has been of interest since de Vries *et al.* investigating the hydration of nitriles to amides with a platinum complex, seeing no retardation to the reaction when pyridines were present decided to look at alternative nucleophiles to water.[48] Moderate to good yields of amides were produced for primary and secondary amines using $[(Me_2PO..H..OPMe_2)PtH(PMe_2OH)]$ as the catalyst with the use of succinonitrile producing predominantly bisamide when two equivalents of amine were added. Whilst the route of activating nitriles with metals to allow for amide formation will be looked at in more detail later, the suggestion of the nitrile intermediate opened up the possibility of a one-pot reaction from a starting aldehyde through to a secondary or tertiary amide of choice. One reported example of this in 2010, from within the Williams group, used a catalyst loading of 5 mol% $NiCl_2.6H_2O$ and utilised hydroxylamine hydrochloride with a base to form the oxime *in situ*, Fig 1.24.[47]

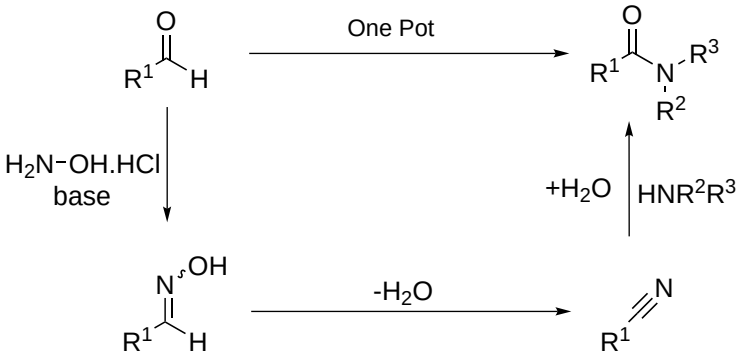


Figure 1.24: One pot oxime rearrangement

Whilst the reaction does not proceed for either ketoximes or oxime ethers the authors showed that a wide range of functional groups on the substrates such as halogens and heterocycles was tolerated. More sterically hindered and less nucleophilic amines proved to be poorer substrates for the reaction and similarly substrates with a second nucleophilic nitrogen site reacted less rapidly, believed to be due to coordination to the nickel.

This work reported above concerning the nickel catalysed rearrangement to form amides built on similar prior work conducted within the group that focussed on "borrowing hydrogen" techniques with a half-sandwich iridium chloride complex. This catalyst was used, along with styrene as a sacrificial hydrogen acceptor, to convert alcohols into aldehydes. These had previously been shown to form imines when attacked by amines which could then be reduced back to the desired secondary amine.[49] The aldehyde intermediate is however also susceptible to attack by hydroxylamine which forms an aldoxime which was shown by Williams *et al.* to be catalysed by the same iridium catalyst to undergo a Beckmann rearrangement to yield the desired amide. Whilst work, previous to this paper mentioned, had shown the catalytic rearrangement of an oxime into an amide, it required a rhodium catalyst at much higher temperatures.[41] Although the isolated yields for amides produced by the iridium catalysed systems were very high after relatively short reaction times, the system did show similar incompatibilities to the nickel chloride transformations whereby ketoximes as well as *O*-alkylated oximes were inert to the reaction. The full scheme depicting the conversion of an alcohol into an amide *via* iridium catalysed oxidation is shown below, Fig. 1.25.[50]

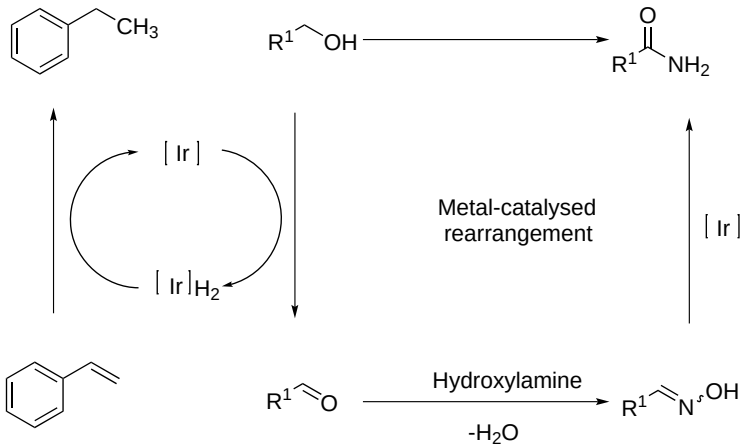


Figure 1.25: Iridium catalysed conversion of an alcohol into a primary amide

1.2.3.6 Transamidation.

The ability to convert one carboxylate amide into another has been known for a long time with the use of the hydrochloride salt of an incoming amine to promote this reaction being reported as early as 1889. This publication initially reported the acylation of hydroxylamine hydrochloride with acetamide and the work was followed up by Elion and colleagues to show that the general acylation of aliphatic and anilinic amines is possible when the amine salt is used with the hydrochloride salts proving favourable due to their relatively low melting points. Upon melting the hydrochloride salt, the precipitation of the formed ammonium chloride was rapidly seen with the reactions proceeding to completion in a matter of minutes and good to excellent yields of the products being reported.[51] Whilst this is a considerable improvement on the purely thermal background reaction there is still the need for high reaction temperatures and the initial formation of the amide salts. For these reasons there have been many investigations into the use of metal salts and alternatives to promote or catalyse this reaction.

The first reported metal promotion of the transamidation of simple amides was published by Bertrand *et al.* with the use of aluminium(III) chloride. This allowed for amide exchange at much lower temperatures than previously reported whilst returning the product in higher yields. The reaction required between 1.3 and 2.3 equivalents of $AlCl_3$ with faster reactions being reported for electron poor amides with even *tert*-butylamine proving possible to acylate in good yields at room temperature when *N*-methylbenzamide was activated by a tosyl group. It was noted by the authors that, as might be expected, primary amides reacted faster than secondary amides although

products from both can be isolated in good yields.[52] Efforts to find a catalytic methodology for transamidation has followed with a lot of the work focussing on hard metals similar to aluminium with particular focus having been placed on the early transition metals in groups(III) and (IV).

One of the first publications using an early transition metal catalyst for transamidation investigated the relative potentials of $Sc(OTf)_3$ and $Ti(NMe_2)_4$ as these two proved the most adept of the catalysts investigated for the transamidation of benzylamine with *N*-phenyl hexanamide. When these two catalysts were investigated for the hexanoylation of a variety of amines there was not a clear cut optimum catalyst. As the authors went on to investigate the transamidation of almost thermoneutral exchange reactions however, it became apparent that the scandium catalyst was unsuitable for these reactions whereas $Al(NMe_2)_3$ as a catalyst proved to be efficient. This suggests that simple Lewis acids can be used when there is a high thermodynamic gain upon the transamidation whereas metal amides have been shown to catalyse thermoneutral transamidations. It is thought that this may be through a bifunctional mechanism with both substrate activation by the Lewis acid as well as nucleophilic attack by a coordinated amide ligand. This second part of the mechanism is suggested by the fact that particularly basic amide anions do not catalytically transamadate under the reaction conditions.

The mechanism of the aluminium(III) catalysed reaction was probed in order to gain mechanistic insights and it again showed the importance of the aluminium for promoting both the amine nucleophile as well as the carboxamide electrophile. The authors have proposed the mechanism seen in Fig. 1.26, the hypothesis of which is supported by kinetic and spectroscopic investigations. Analysis of NMR data shows that the catalytic cycle begins with the tris-amido species of the initial amide substrate, when this was allowed to reach equilibrium, with addition of the amine, there was a spread of carboxylate ratios attached to the aluminium centre. These appeared in the order designated in the mechanistic cycle and which came close to matching the statistical ratio of 1:3:3:1 that would be expected in a thermoneutral transamidation. The slight alteration from this distribution was attributed to a greater affinity of *N*-benzylamidate for Al(III) over a proton than the *N*-(2-ethylhexyl)amidate anion that was the incoming amine in the reaction. The rate of the reaction was found to be independent of the concentration of carboximide however when the absolute quantities of the reagents was maintained and the volume of solvent varied it was seen that the rate of reaction varied with the square of concentration of solvent suggesting a bimolecular rate law. Investigating the individual effects of varying initial concentrations of the reagents on the reaction rate it was determined that the rate law was: $rate = k[Al^{(III)}][RNH_2]$. Interestingly the authors

report near identical product ratios when the reaction was run in reverse, suggesting the equilibrium point had been reached.[53]

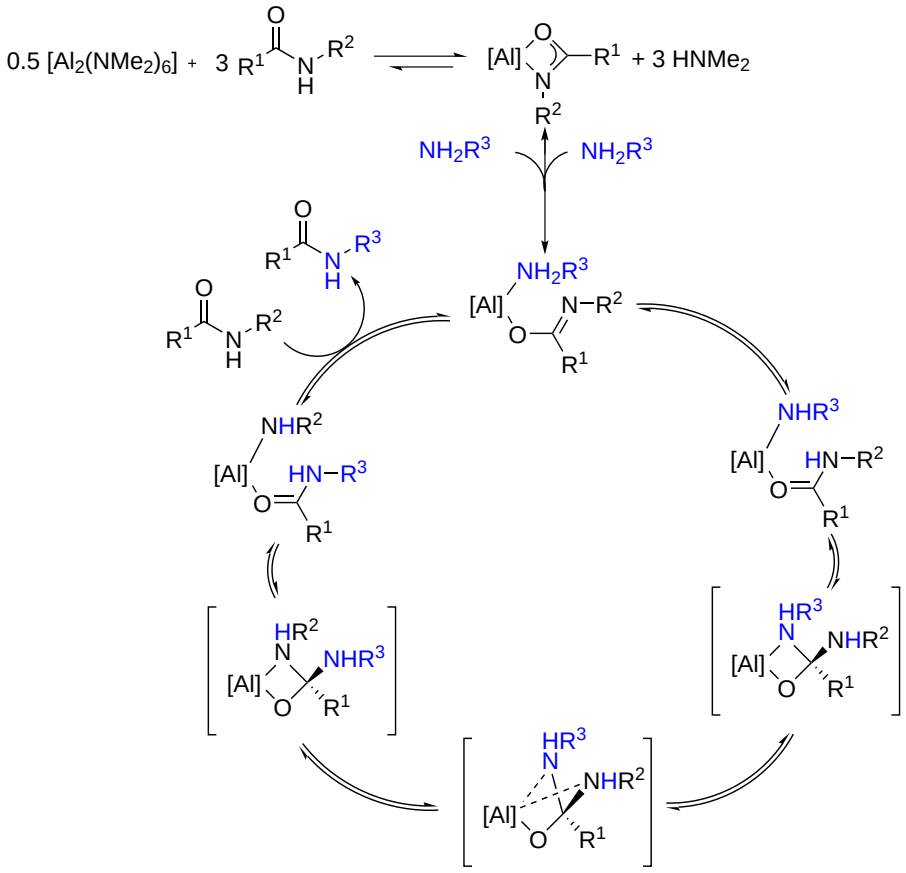


Figure 1.26: Aluminium catalysed transamidation mechanism

Work focussing on the hard early transition metals was further looked at by the same group, investigating the variation that using different titanium compounds, as catalysts, could have on the nature of the reaction with some catalysts promoting transamidation whereas others favoured amidine formation. $Ti(NMe_2)_4$ as described above is an efficient and highly selective catalyst for the transamidation reaction and is generally used at catalyst loadings of 20 mol% and below. The use of Cp* ligands around the titanium centre however were shown to hinder the transamidation reaction and when the compound was used as a stoichiometric additive it was shown that high selectivities for the amidine formation reaction could instead be achieved. The postulated reaction mechanism for this is given in Fig. 1.27, and it is believed that the 4 membered transition state undergoes retro-cycloaddition to yield the oxotitanium species which is very thermodynamically stable. Under catalytic conditions the titanium is more likely

to form a tetrakis(amidate)Ti(IV) species as there will be a greater concentration of carboxamide. This excess of carboxamide is proposed to inhibit the formation of the imidotitanium species. The transamidation mechanism is believed to differ at this stage of the reaction mechanism with the addition of either an external primary amine to the bound amidate to give a zwitterionic intermediate followed by proton transfer to form a metallocycle. Alternatively there could be intramolecular attack of a bound amido ligand to give the neutral species that can form the same metallocycle. The Ti-N bond of the metallocycle is weakened by protonation of the nitrogen allowing for more facile exchange of the amino fragments which enables the transamidation.[54]

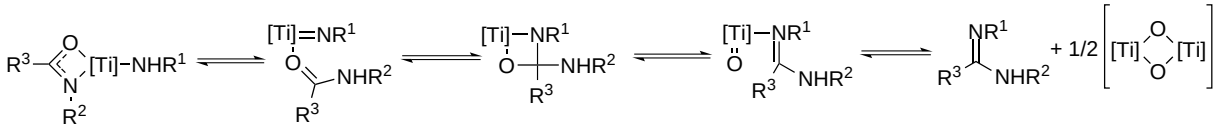


Figure 1.27: Titanium mediated formation of amidines

This work was extended so as to be able to carry out selective transamidations under more ambient temperatures to enhance the applicability of the methodology. It was found that the use of $Zr(NMe_2)_4$ in toluene could catalyse both the transamidation of tertiary amides and could also catalyse the related amide metathesis reactions *via* sequential transamidation steps.[55]

There have been alternative catalysts used for transamidation reactions other than the hard group(IV) and (XIII) metals, including some heterogeneous examples such as the CeO_2 catalysed solvent free transamidation reported by Satsuma *et al.* [56] and the use of non-metal catalysts such as boric acid [57], or hypervalent iodine.[58] One recent very interesting paper uses the inexpensive and readily available L-proline as a catalyst for the transamidation of a wide array of mostly primary amides in good to excellent yields although some secondary amides were also investigated with less successful conversions being reported. Although the use of non-metal catalysts does have inherent benefits, in particular in removal of the catalyst, the authors did report the necessity of high reaction temperatures and long reaction times. The reaction mechanism proposed by the authors which is shown in Fig. 1.28, indicates attack of the carbonyl of the amide by the L-proline enhancing its electrophilicity and increasing its susceptibility to attack by an incoming amine.[59] The mechanism proposed proceding through an amidine intermediate with loss of water rather than ammonia seems unlikely and so an alternative route could involve the proline acting as a hydrogen donor.

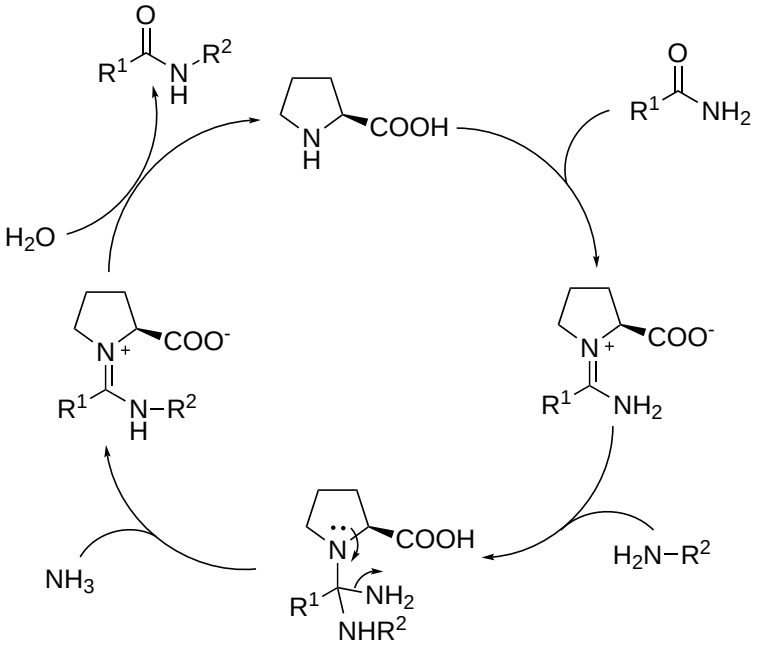


Figure 1.28: Proposed L-proline catalysed transamidation mechanism

1.2.3.7 Amides from nitriles.

The use of nitriles in the catalytic formations of amides has been relatively sporadically investigated with the majority of work having looked at the hydration of nitriles into the corresponding primary amide. Although the unique nature of the carbon-nitrogen triple bond in nitriles does also allow for both electrophilic and nucleophilic attack to form amide bonds, the latter, shown in Fig. 1.29, is by far the more common. Acid and base catalysis for the formation of the primary amide has been known about for a very long time, both can however present problems with over-reaction. In the case of base catalysis there is the possibility of cleaving the formed amide under the basic conditions to liberate ammonia and form the corresponding carboxylate salt whilst acid catalysis runs the increased risk of polymerisation. Metal catalysts can demonstrate a facile route to rapid and favourable formation of the amide product.

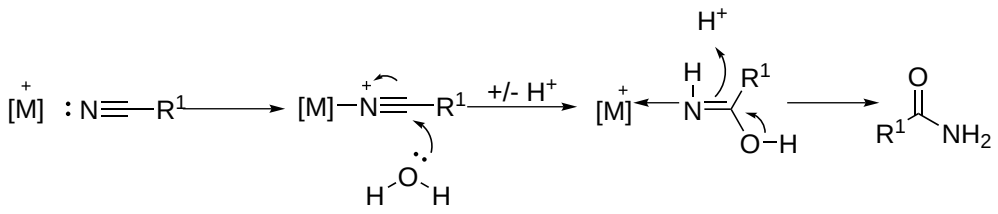


Figure 1.29: Nucleophilic attack on metal bound nitriles

The use of metal catalysts has been shown to increase the rate of base hydration of nitriles commonly by a factor of between 10^6 and 10^{10}.[60] The majority of literature revolves around the metals; platinum, rhodium and palladium although ruthenium, iridium and rhenium have become of greater interest recently. Some of the most active catalysts are based on platinum(II) phosphinito complexes [61] although many more affordable metals have also demonstrated catalytic activity such as; zinc, nickel, titanium, cobalt and copper. One of the factors in the metal catalysed hydration of nitriles is the oxidation state of the metal and can demonstrate some of the greatest difference in reaction rates between otherwise similar or analogous systems. An example of this is the case of the pentavalent ruthenium compounds; $[Ru(II)(NH_3)_5]$ and $[Ru(III)(NH_3)_5]$ whereby the former has no effect on the rate of hydration of acetonitrile to acetamide whilst the Ru(III) compound enhanced the rate by two orders of magnitude compared with the free nitrile. A postulated reasoning behind the Ru(II) catalyst having no perceptible effect on the rate of catalysis is that there would be a much greater level of π-back bonding to the nitrile. This is due to the ruthenium(II) being less electron positive and so increasing the electron density on the carbon atom thus decreasing its susceptibility to nucleophilic attack. It is noteworthy that a paper from Katz *et al.*[62] showed that whilst the ruthenium(II) complexes are by nature less reactive than the ruthenium(III) catalysts for the reasons covered, there is still latent potential for use that can be exploited by the use of appropriate ligands. The catalyst investigated by the authors was a d^6 Ru(II) complex with multidentate π-acceptor ligands, $[(terpy)(bipy)Ru]^{2+}$ which hydrated acetonitrile at a rate of approximately 10^2 times greater than a homologous ruthenium compound with poor π-accepting ligands.

Similarly the overall charge on the complex ion can also play a role in affecting the activation of nitriles with the general rule being; the higher the overall charge then the greater the activation of the nitrile towards hydration.[60] In a lot of cases however the experiments cannot necessarily be compared directly; an example of this is the hydration of acetonitrile by platinum complexes reported in the paper by Lippert where the catalysts i) $[Pt(NH_3)_2Cl_2]$ and ii) $[PtCl(NH_3)_2(MeCN)]^+$ were compared.[63]

Nitriles can also be used to produce non-primary amines. One of the earliest methods

reported of this was by Ritter *et al.* where in this instance the nitrile is acting as the nucleophile rather than undergoing attack. In the first reported instance, an alkene was activated by stoichiometric sulfuric acid before attack by the nitrile and subsequent hydration to the *tert*-butyl amide as shown in Fig. 1.30.[64]

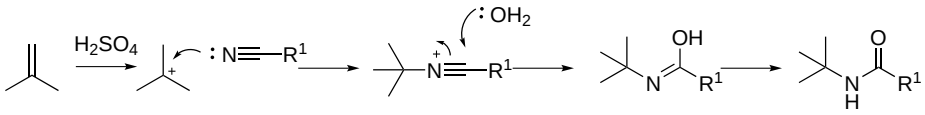


Figure 1.30: Ritter reaction

Many reactions however will not tolerate concentrated sulfuric acid for either solubility or degradation reasons, and in 2006 Barrett *et al.* reported the production of *N*-*tert*-alkyl and aryl amides from a Ritter reaction with tertiary alcohols on nitriles using a catalytic amount of bismuth triflate.[65] A variety of metal triflates was looked at by the authors to catalyse the addition of *tert*-butanol to benzonitrile but only $Bi(OTf)_3$ compared favourably with triflic acid. The conversion of both aliphatic and aromatic nitriles were seen to be converted in moderate to good yields and a wide range of functional group tolerance was also seen. Similarly using benzonitrile as the control nitrile a range of tertiary alcohols were also tested giving good yields even for sterically demanding substrates. The authors noted that whilst a range of solvents was investigated as media for solid nitriles, only nitrobenzene proved applicable and also worked as an additive for a range of nitrile couplings to *tert*-butanol.

Recently a particularly inexpensive synthesis of a variety of amides has been shown by Cossy *et al.* whereby an iron chloride salt is used to catalyse the Ritter reaction in the presence of two equivalents of water at relatively high temperatures.[66] This high temperature of 150 °C (reflux in cumene) was required to limit the formation of ethers as a side reaction which limited the yield of amide to 72% after six hours when run in toluene at 110 °C for the control reaction. The authors chose to focus particularly on the formation of *tert*-butyl amides as they can be synthetically valuable due to their ability to be deprotected to yield the corresponding primary amide. It was noted that *tert*-BuOH gave a low conversion of benzonitrile using the $FeCl_3.6H_2O$ catalyst whereas *tert*-butylacetate was seen to be a far better source of the *tert*-butyl carbocation. Iron catalysts including $FeCl_3.6H_2O$ have been seen to produce ethers in previous literature as well as having been reported as a background reaction in this paper leading the authors to give the following scheme as a proposed mechanism; whereby the benzylic carbocation that could be part of the ether formation is trapped by acetonitrile to yield the amide after hydrolysis. It is however possible that the acetonitrile might attack either of the other transitional products as shown in Fig. 1.31 to yield the same amide.[66]

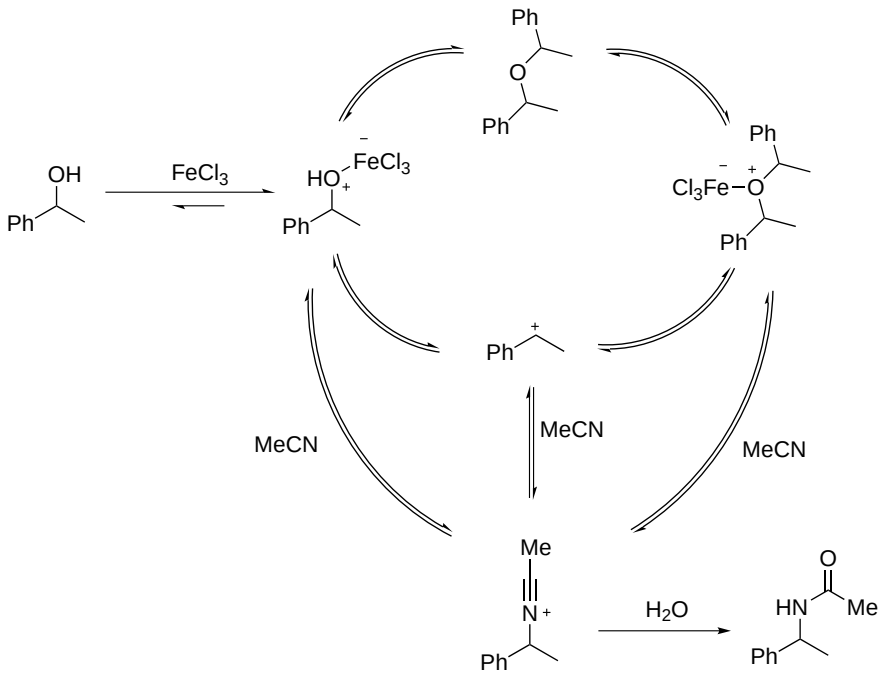


Figure 1.31: Iron chloride catalysed Ritter reaction

The addition of organonitriles to alcohols is not the only pathway to amides from nitriles. As early as the late 1800s Pinner had been investigating the formation of related compounds such as amidines and esters from the addition of HCl or HBr to nitriles.[67] Approximately one hundred years later the first significant attempts to catalyse this process were investigated and a report, by Murahashi *et al.* described a general method for the conversion of amines with nitriles to amides under neutral conditions.[68] This process utilises a ruthenium(II) catalyst (namely $RuH_2(PPh)_4$) and proceeds cleanly and with high efficiency in a single step although it does require high reaction temperatures. The general reaction parameters proposed by the authors include a slight excess of amine to nitrile, 3 mol% of the catalyst with two equivalents of water in DME solution. The reaction was left for 24 hours at 160 °C under an argon atmosphere. The authors decided to explore the relative chemo-selectivity between primary and secondary amines and one of these reactions involved the coupling of benzylcyanide with dipropylenetriamine which produced an 86% yield of $N1$,$N7$-bis(phenyl-acetyl)dipropylenetriamine with a mere 3% of the triacyl compound. Fig. 1.32.[68]

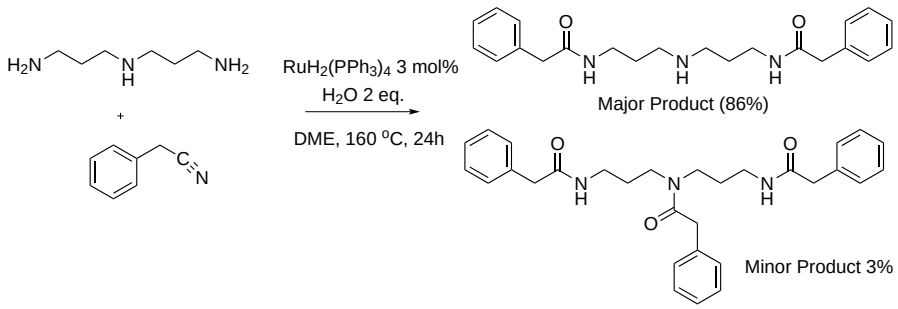


Figure 1.32: Chemoselective acylation of primary amines by nitriles

A report published in 2009 by Williams *et al.* showed a particularly inexpensive method for the process of amine acylation by nitriles.[69] The two catalysts reported were the inexpensive and readily available; $FeCl_2.4H_2O$ and $Fe(NO_3)_3.9H_2O$. Surprisingly it was noted by the authors that the iron(III) salt was less successful although one might have assumed it would have greater Lewis acidity and hence greater efficiency in nitrile activation. It was reported that the use of solvents, and in particular non-polar solvents, led to a significant reduction in conversion. Furthermore the authors noted the ability of both catalysts to form imine on the absence of nitrile although it was noted that only minimal imine formation was seen for the intended reaction. The general reactivity patterns of the substrates investigated in the paper followed a combination of steric and electronic effects in which unbranched primary amines formed secondary amides with ease. Benzylamine and analogous substituted variants thereof reacted with high conversions whereas less nucleophilic aniline gave very little conversion to the amide when reacted with propionitrile. More bulky amines such as *tert*-butylamine produced no amide after 24 h at 125 °C. In such cases where, due to either steric or electronic deactivation, there was no production of secondary or tertiary amide the authors reported significant amounts of primary amide formed by hydration instead.

There are two proposed mechanisms for the formation of secondary and tertiary amides from the nitrile precursor. The first involves the hydration of the nitrile to a primary amide followed by transamidation with the loss of ammonia upon attack by the incoming amine. The second pathway proposed involves formation of an intermediate amidine which is then hydrolysed, again with the loss of ammonia, to yield the desired amide. Of these two routes the Williams paper appears to support this latter hypothesis. When an amine was added to the primary amide which would be formed initially by the hydration of a nitrile and subjected to the same reaction conditions there was a low conversion to the secondary amide which suggests this is not the predominant route being followed although it may be a minor pathway. One other pathway that was dismissed by the authors was a Ritter type reaction *via* a carbocation. This was decided to be

unlikely as the *tert*-butylamine gave no reaction despite its propensity to form a tertiary carbocation and therefore the amidine pathway, Pathway 1 in Fig. 1.33, was held to be the major route for amide production.

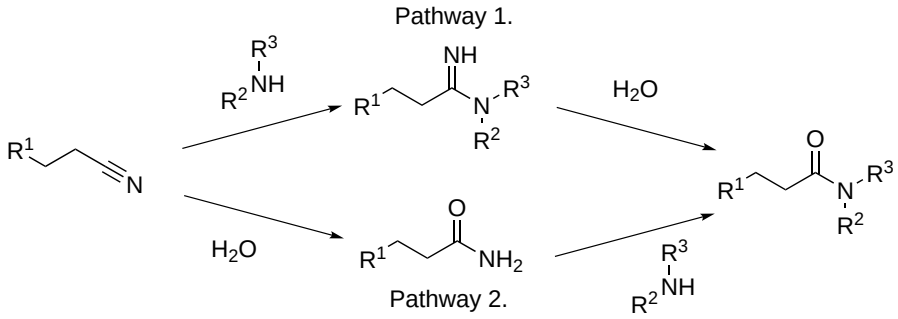


Figure 1.33: Potential intermediates in amide formation

Within the last year an alternative metal catalyst has been shown to catalyse the acylation of primary aliphatic and aromatic amines with nitriles in average to good isolated yields whilst conducting the reaction in water. The catalyst reported was copper acetate (10 mol%) with the use of 2-piperidine carboxylic acid as a ligand. The reactions were conducted at 100 °C and it was surprising to see that an increase in temperature did not result in an increase in yield whereas lowering of the reaction temperature severely reduced the reactivity.[70]

1.2.3.8 Amides from esters.

Whilst there has been a plethora of reports of the catalytic synthesis of amides from a wide variety of starting materials and through a variety of different mechanism, there is comparatively little literature on the acylations of amines with esters acting as the acyl donor. One of the primary reasons for this disparity is that although the process is generally thermodynamically favourable, due to formation of a strong amide bond, the stability of the starting ester means that the activation energy required for amidation is remarkably high and therefore generally requires high temperatures to initiate reactions. There have been many attempts to find routes for the aminolysis of esters at lower temperatures in shorter times and mostly these investigations have focussed on the use of stoichiometric transition and s-block metals which have more recently been overlooked in favour of metal catalysed routes. In the past few years there has also been a shift in focus towards highly active organo-acyl transfer reagents which will be discussed below. It is worth mentioning however that as early as 1939, Audrieth and co-workers described the conversion of simple esters to the *N*-cyclohexyl amide counterparts utilising 40 mol%

of the hydroiodo salt of cyclohexylamine. Whilst the reactions were conducted at room temperature, the reaction times of over 100 h for the most facile of substrates meant that the process was not adopted on a wide scale.[71]

Some of the earliest metal mediated amide synthesis were conducted by Weinreb *et al.* with the use of an aluminium amide formed *in situ* from the trimethylaluminuim precursor.[72] A one to one mixture of the Me_3Al with either liquid ammonia or a primary or secondary amine formed the dimethylaluminium amide, this was then reacted with the ester to produce high yields of the amide in 12-48 h showing the ability to produce primary secondary or tertiary amides albeit with a limited substrate scope. Alternative metals have been investigated to promote the formation of amides from esters including several early tin mediated reports. Leppart *et al.* reported the reaction of aminostannanes against a wide variety of different functional groups including mono- and di-ethylesters to yield the corresponding amides with stoichiometric tin ethoxides.[73] More recently Roskamp and co-workers showed how a mixed tin amide species, formed from the *in situ* addition of an amine to a [bis(bis(trimethylsilyl)amino]tin (II) complex, could produce a wide range of secondary and tertiary amines at room temperature within 12 h. It was noted by the authors that when using β-hydroxy esters alteration of the reaction conditions could be used to create different products in high yields. Fig. 1.34.[74] Other metals have been investigated for the stoichiometric metal promoted aminolysis reaction including, magnesium [75], lithium [76] and sodium both as a basic salt [77],[78] and also as the simple stoichiometric alkoxide [79] although there is a significant limitation of using such reactive species on functionalised substrates.

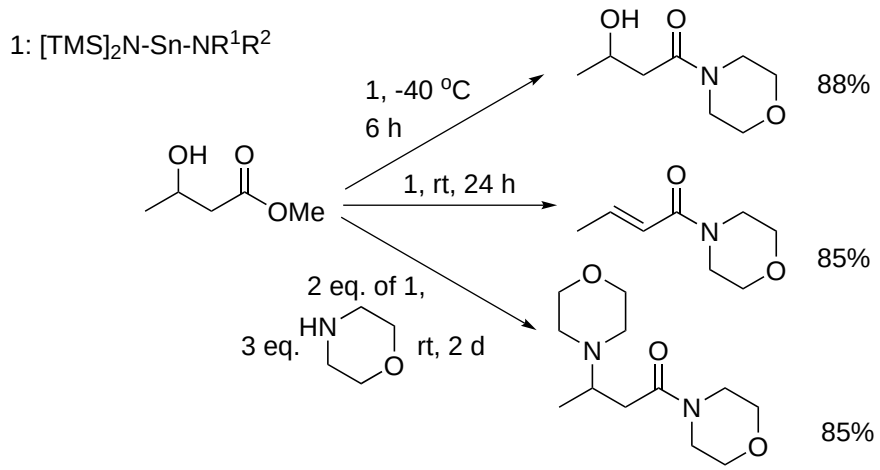


Figure 1.34: Possible products from tin amide aminolysis

One of the first truly catalytic methods for the amidation of esters was reported by Nomura and co-workers based around a triphenylantimonydiacetate complex. After initially forming acetamides stoichimetrically in mostly very high yields, the exception being for *tert*-butylamine, the authors investigated the potential of regenerating the active antimony species *in situ*. It was shown in the publication that the addition of acetic acid allowed for the quantitative formation of amide with only 10 mol% catalyst loadings and only a slight excess of amine.[80] An example of this methodology being used in the synthesis of a natural product is given by Yamamoto and co-workers in their synthesis of Spermine derivatives where the antimony centre was used to act both as a template in the microlactamisation of tetra-aminoesters and to catalyse the aminolysis.[81]

One of the seminal publications in the field of ester-aminolysis was published by Ranu in 2003 where the ability to produce secondary amides with a catalytic amount of indium triiodidie was described in a simple elegant methodology. Whilst both anilinic and benzylic nucleophiles were tolerated along with many functional groups on the ester substrate, the authors note the limitations in producing primary or tertiary amides under the system. Although not looking into the mechanism in detail it was revealed that indium alone did not catalyse the reaction and the addition of iodide produced conversions of only between five and ten percent.[82]

The use of group(IV) alkoxide-additive complexes as highly active catalysts for the acylation of amines with esters has been investigated by the group of Porco *et al.* for several years now after their initial paper in 2005. In this publication they show the propensity of a range of group(IV) metal alkoxides to catalyse the aminolysis reaction although none showed a marked increase over Ti(O*i*-Pr)$_4$ until the addition of *O*-based activators. A range of activators was screened against the group(IV) alkoxides (O-^{i}Pr or O-^{t}Bu) and it was found that zirconium-*tert*-butoxide in conjunction with HOAt additive gave the greatest conversions although the cheaper HOBt was also effective. The methodology was shown to be suitable for both acid and base sensitive functional groups with the exception of the very base sensitive Fmoc group and showed good chemoselectivity especially for aromatic amines of aliphatic alcohols. The key disadvantages with this methodology is that the reactions are commonly run at 60 °C or 100 °C, although some would couple at room temperature, with reaction times commonly between 12-48 h. A mechanism was proposed by the authors, Fig. 1.35, based on X-ray crystallographic analysis and NMR studies with kinetic *in situ* FTIR studies suggesting the reaction rate exhibited first order dependence on both amine and ester concentration at catalyst loadings of 5 mol% with the reaction also appearing to be first order in zirconium.[83]

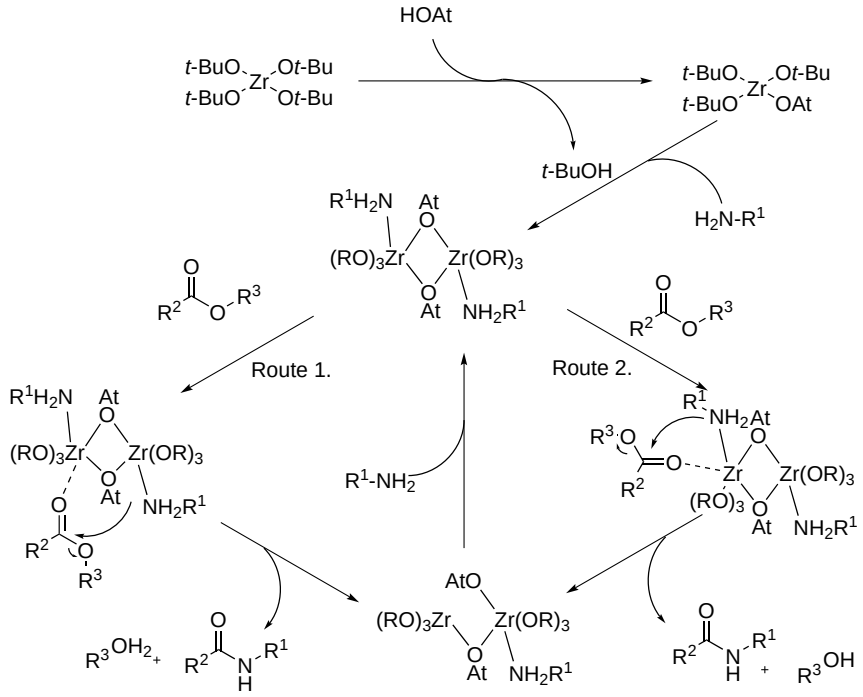


Figure 1.35: Mechanism for $Zr(O^tBu)_4$ with HOAt additive formation of amides

Following this publication the group expanded the substrate scope to investigate the applicability of the reaction for converting dialkyl-carbonates into carbamates and then further into unsymmetrical ureas. Investigations began with optimisation of the additive for the zirconium *tert*-butoxide catalyst specifically for the conversion of carbonates to carbamates. In this case 2-hydroxypyridine was found to be the best and was utilised to convert a range of symmetrical carbonates demonstrating good selectivity for the mono-substitution and good functional group tolerance with the ability to di-acylate diamines using the methodology working for both light (MeOH, EtOH) and heavy alcohols (BnOH). The authors then moved on to determine the optimum conditions for the amidation of urethene as their standard substrate; it was found that zirconium *tert*-butoxide with 4-methyl-2-hydroxyquinoline produced markedly better results than the other additives. Again a wide range of amine nucleophiles and varied carbamates were reacted to form; symmetrical, cyclical and unsymmetrical ureas.[84] Interestingly the group that developed this methodology went on to use it in the synthesis of macrocyclic bislactams for the intermolecular coupling of two enantiomerically pure α,β-unsaturated amino-esters to form a bis-lactam in 80% yield that could undergo base catalysed cyclizations as shown in Fig. 1.36.[85]

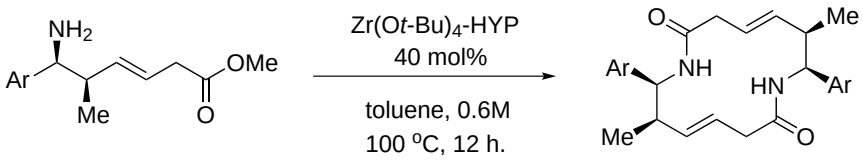


Figure 1.36: Application of $Zr(O^tBu)_4$-HYP

A recent paper has further shown the useful application of simple more readily available salts of inexpensive group(I) and (II) metals. One particularly industrially relevant paper by Abaee and co-workers described the use of lithium bromide for the recyclable catalytic aminolysis of esters. The benefit of simple filtration to recover the lithium bromide, which showed only marginal decreases in reactivity over the five uses reported, was supported by a methodology that was conducted at room temperature albeit over relatively long periods of time.[86] Alternatively the use of s-block alkoxides has been described in the literature by Wright and co-workers who focussed on the group(II) Lewis acids, primarily $Mg(OMe)_2$ as well as the salt calcium chloride.[87] It had been suggested in the literature previously that Mg_3N_2 could be used as a solid source of ammonia when placed in simple alcohols as there is an endothermic reaction to protonate the nitrogen to yield ammonia and the corresponding magnesium alxoxide. As this ammonia was able to form the amide in surprisingly good yields from methyl esters that were present, it was thought that the magnesium salt may be playing a role.[88] A screen of Lewis acid salts by Wright *et al.* showed the two mentioned catalysts to be most applicable for the aminolysis reaction and although anhydrous cerium and magnesium chlorides did give good conversions their hygroscopicity limited their practical usage. A screen of suitable substrates demonstrated compatibility with a range of functional groups, including but not limited to nitro, alcohol, phosphines, sulfonamides, heterocycles as well as accommodating steric bulk around the ester. One of the key benefits noted by the authors over the previous methodology was the avoidance of over pressurization and explosion risk, produced by the endotherm created by the use of magnesium nitride.[87]

Similar methodologies investigated the use of sodium ethoxide [89] and sodium methoxide [90] catalysts building on reports of their stoichiometric use. Whilst these catalysts were effective in even low catalyst loadings one particularly significant point highlighted by the authors was that for challenging substrates with racemisable α-positions, the basic conditions led to a decrease in enantiomeric excess in the amide produced. In order to elucidate a solution to this problem the authors screened a variety of acidic alcohols that could be added to counteract the basicity of the reaction medium and found that 10 mol% NaOMe with 30 mol% trifluoromethylphenol proved to give the best yields whilst maintaining stereochemical integrity, (Fig. 1.37).

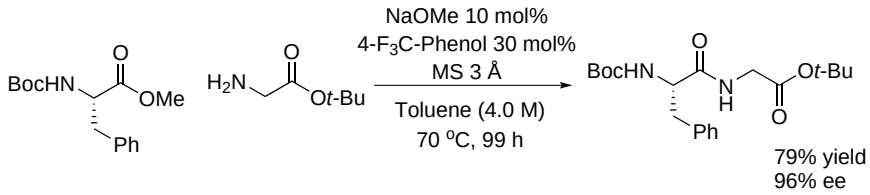


Figure 1.37: Sodium methoxide with additive catalysed amide bond formation

One final example of metal catalysed amide formation from esters was reported in 2011 by Milstein and co-workers. Using a similar PNN pincer complex to that reported for the formation of amides from acids, Fig 1.16, they describe the conversion of esters into amides with the addition of two equivalents of amine and the loss of dihydrogen. A substrate scope of primarily cyclic secondary amines was investigated along with two examples of primary amines and for the most part they showed very high conversions although in some cases high temperatures and longer reaction times were required. A postulated mechanism is given below and whilst the authors believe they do not yet have sufficient data they feel that it accounts for some of the anomalies seen in the reaction scope. One such anomaly is the very high efficiency of the PNN ligands (TON of *ca.* 1000) whilst the very similar PNP ligands are catalytically inert under the reaction conditions. This is attributed to the intrinsic hemi-lability of one arm of the PNN ligand that allows for association of both amine and ester as shown in structure B in Fig. 1.38, which is not possible in the PNP ligated catalyst. It is important to note the limitation of this methodology in that it requires the use of symmetrical esters or the use of a sacrificial equivalent of amine.[91]

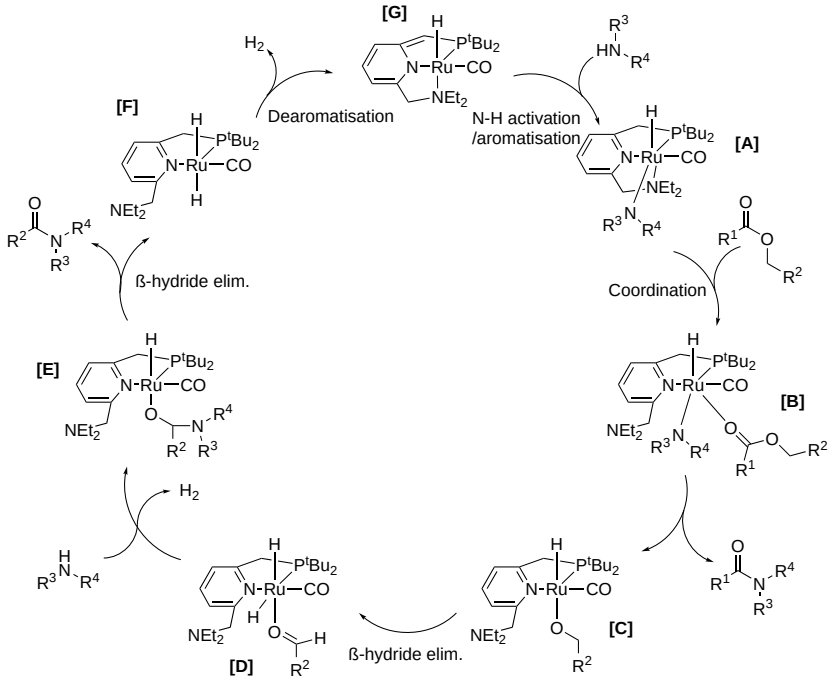


Figure 1.38: Milstein's proposed ester-amidation mechanism

1.2.3.9 Summary

The formation of amides through the direct thermal coupling of an amine with a carboxylic acid has been recorded since the early 20^{th}century with examples of the use of acid chlorides as an activated carbonyl having been reported even earlier. These reactions have the detrimental aspects of either requiring very forcing reaction conditions to proceed or producing stoichiometric amounts of harmful waste products.

There have been many attempts in the intervening time to find alternative ways in which to form amides, using a wide variety of starting substrates and the use of various additives or catalysts. Metallic, non-metallic as well as organo-catalysts have all been investigated in an attempt to develop a robust, mild and atom efficient method for the production of biologically relevant amides from readily available chemical feedstocks.

Whilst there has been some interesting literature on the aminolysis of esters for the most part either a stoichiometric promoter, such as a main group metal-amide, is required or the use of harsh reaction conditions for some of the catalytic methodologies which could limit reaction scope. As the ester moiety is so ubiquitous in both Nature and current organic synthesis a mild catalytic method for the production of a variety of amides from esters would be useful for industrial purposes. Some work focusing on group(IV) metals in particular zirconium has shown some potential but removal of the need for an expensive additive such as HOAt would be preferable.

1.3 Results and Discussion

1.3.1 Previous work and introduction.

Within the group the use of zirconium salts for the formation of amides has been looked into in detail. Initially the use of $ZrCl_4$ and Cp_2ZrCl_2 for the direct coupling of carboxylic acids with amines was reported by Allen *et al.*[12] It was demonstrated that a wide range of amides was accessible using this methodology with a range of functional groups including; esters, nitriles, heterocycles and protecting groups. In most cases the reaction times could be dropped from 22 h to 4 or 5 h upon the addition of the catalyst with Cp_2ZrCl_2 generally proving the more effective of the two. Later in the year Atkinson *et al.* reported the use of the same Cp_2ZrCl_2 catalyst for the highly active transamidation of primary amides to secondary or tertiary amides in cyclohexane.[92] A series of kinetic experiments was conducted in order to elucidate the reaction mechanism and it was seen that the reaction rate was first order in zirconocene dichloride and starting amide but second order in benzylamine. This led to the proposed reaction scheme, seen in Fig. 1.39, which accounts for the two molecules of benzylamine and goes some way to explaining the reactivity. Some isotope effects were looked at and it was shown that the nitrogen in the final product comes from the incoming amine as expected and the use of D_3CONH_2 suggests that the reaction does not proceed *via* elimination of ammonia to form a ketene intermediate that undergoes nucleophilic attack.

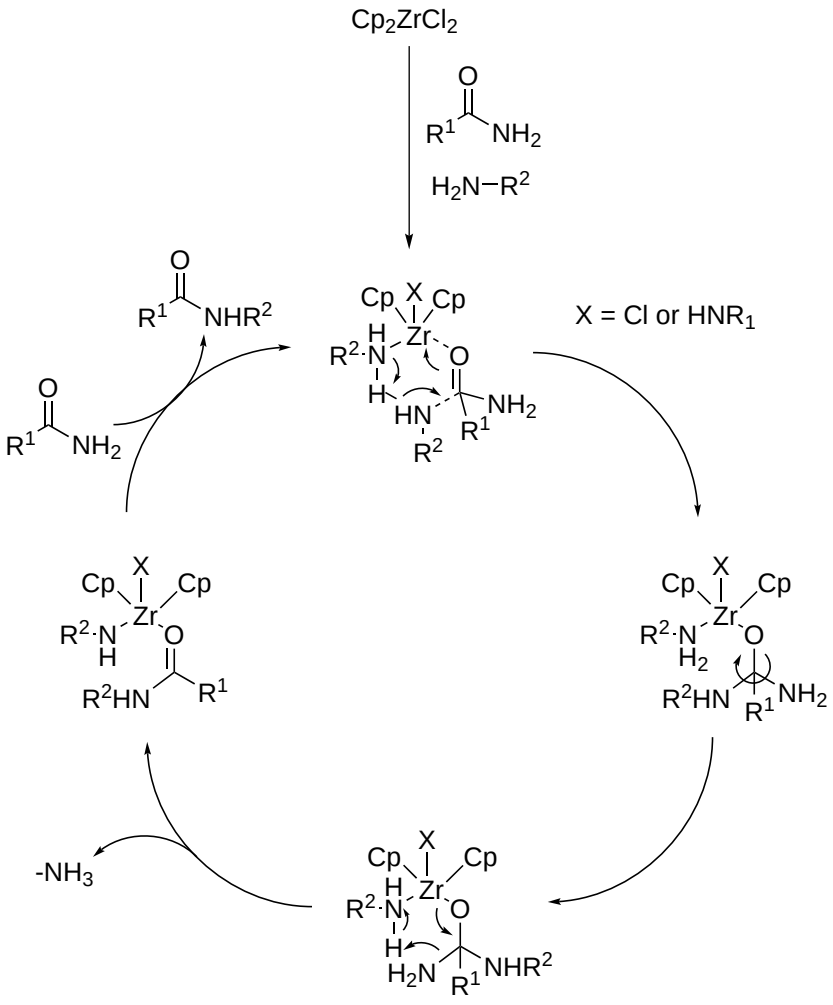


Figure 1.39: Proposed transamidation mechanism catalysed by zirconocene dichloride

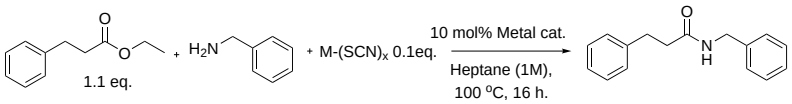
In more recent, as yet unpublished work, it has been found that the addition of an additive can further enhance the rate of the reaction and in particular the use of thio- and isothiocyanate salts. It is thought that in this reaction the thiocyanate ligands interact with the zirconium rather than directly on the substrates to form more reactive acyl species. In the case of transamidation it is believed that the thiocyanate ligand might possibly be activating the incoming nucleophiles through hydrogen bonding and increasing the nucleophilicity.

Robust methodologies have been described above for the acylation of amines from both carboxylic acids and primary amides and one of the surprising points of note was that in certain cases more mild conditions could be used to acylate using the structurally far more stable amide. No attempts however have been made to acylate using esters within the group and indeed as can be seen from the introduction they remain an

under-developed feedstock for the production of amides due to their robust nature and resilience to aminolysis. What follows is an account of the optimisation and application of the acylation of amines by esters catalysed by zirconocene dichloride.

1.3.2 Optimisation.

The first stage of optimisation involved building on the work within the group that showed the addition of a thiocyanate additive increases the rate of zirconocene dichloride catalysed transamidation. In order to determine if it was possible to extend this methodology to the aminolysis of esters a range of Lewis acids was screened against some common thiocyanate salts in a chosen standard reaction with the results given in Table 1.1.



	Percent Conversion by ^{1}H NMR			
Metal catalyst (10 mol%)	NH_4SCN	AgSCN	NaSCN	No additive
$Sc(OTf)_3$	27	-	16	30
MgI_2	21	5	16	35
KI	5	0	-	-
$Al(O^iPr)_3$	12	12	-	-
$ZrCl_4$	30	29	33	50
$Ni(OAc)_2$	10	-	3	3
$ZnCl_2$	6	5	-	-
$TiCl_4$	-	11	-	-
Cp_2ZrCl_2	-	84	81	40
$In(OTf)_3$	-	-	8	7
AgOTf	-	-	3	-
No catalyst	6	2	2	2

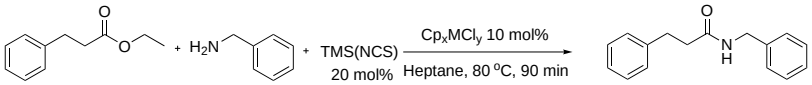
Table 1.1: Thiocyanate additive screen

What can clearly be seen from the reactions run with ammonium thiocyanate as the additive is that the zirconium tetrachloride along with the scandium(III) triflate were the most impressive catalysts whilst the thiocyanate on its own did little. From this reaction set the other thiocyanates were screened against a slightly altered Lewis acid array to reflect the initial good catalysts. This included the addition of Cp_2ZrCl_2 to determine whether it out-performed zirconium tetrachloride which it did markedly with both silver- and sodium-thiocyanate. The final column shows the catalytic effect of the Lewis acids without any thiocyanate additives; it's immediately noticeable that in the

vast majority of cases the addition of an additive acts to retard the reaction including in the case of zirconium tetrachloride. Conversions using zirconocene dichloride with a thiocyanate additive on the other hand are very significantly improved, 84% with AgSCN and 40% conversion with just zirconocene dichloride. As none of the thiocyanates alone showed any particular enhancement to reaction rate it suggests that a synergistic effect between the zirconocene and the thiocyanates occurs and that both are required for optimum conversions.

As the group(IV) metals demonstrated good catalytic activity for the conversion of the ester into an amide, several attempts were made to investigate the use of titanium catalysts as alternatives to zirconium because titanium compounds are generally cheaper and more readily available than their heavier analogues and known to act as a good Lewis acid. The use of titanium(IV) isopropoxide with a screen of four different thiocyanates showed that in all cases the additive hindered the reaction rather than increasing the catalytic efficacy and even when KSCN, which showed the least retardation to the reaction, was investigated in a range of different solvents there was no real improvement on the use of only $Ti(O\textit{i}\text{-}Pr)_4$. Of the titanium precursors tried only titanocene dichloride showed any improvement upon the addition of a thiocyanate, conversion increasing from 5% to 9% with the addition of AgSCN. Although alternative solvents were investigated, with non-polar solvents again proving the most effective, there was insufficient conversions to compete with the zirconium catalysts.

As the initial metal screen had shown that only the cyclopentadienyl, organometallic zirconium catalyst was activated by thiocyanates and not the simple chloride salts, it was decided to investigate similar metallocene complexes to determine if an improvement could be made to or around the metal centre, the result for which are shown in Table 1.2. Trimethylsilyl isothiocyanate was chosen as the additive as it had demonstrated some potential for transamidation, is anhydrous and appeared to dissolve in heptane negating some practical considerations that could have caused experimental inconsistencies.

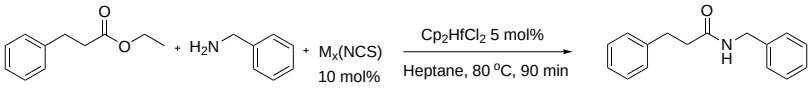


Entry	Metallocene Catalyst	Percentage Conversion by ^{1}H NMR
1	Cp_2ZrCl_2	33
2	(ethylene bisindenyl)$ZrCl_2$	29
3	$CpZrCl_3$	19
4	$Cp^*_2ZrCl_2$	14
5	Cp_2HfCl_2	42
6	Cp_2NbCl_2	4

Table 1.2: Screen of metallocene catalysts

The data shows that increasing the steric bulk around the cyclopentadienyl decreases the reactivity relative to the standard zirconocene dichloride, entries 2 & 4 Table 1.2, whilst the mono-cyclopentadienyl zirconium catalyst was also ineffective. Changing the central metal atom by contrast had a dramatic effect on conversions, the use of the d^1 complex, niobocene dichloride, showed only minimal catalytic activity. Comparatively replacement of the zirconium with hafnium, entry 5 Table 1.2, showed an interesting increase in conversion which was somewhat surprising considering the similar chemistries expected of hafnium and zirconium, a result of the lanthanide contraction.

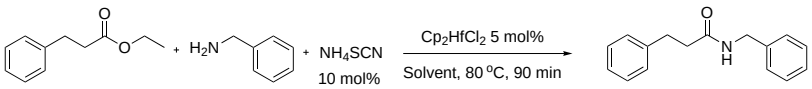
Taking this information forward experiments were carried out to determine the optimal thiocyanate additive for the hafnocene catalyst. Of the available additives investigated it was seen that ammonium thiocyanate gave the highest conversions with sodium thiocyanate the next best, Table 1.3. These reactions were conducted by purging the solids under argon at 80 °C for 15 minutes to remove some of the residual moisture and by utilising dry solvent.



Entry	(*iso*)-Thiocyanate	Percent Conversion by ^{1}H NMR
1	NH_4SCN	68
2	KSCN	51
3	NaSCN	57
4	AgSCN	47
5	^{t}BuN(SCN)	38
6	TMS(NCS)	42
7	No additive	27

Table 1.3: Hafnocene with thiocyanate screen

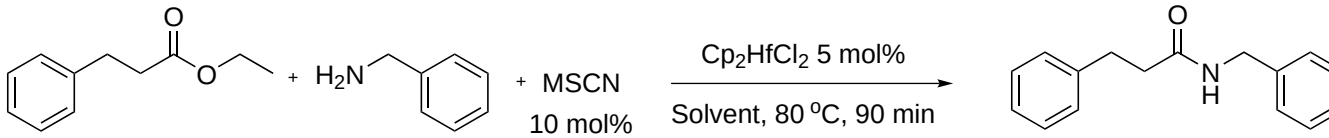
The next step was to determine the optimum solvent, in this experiment the reagents were all added together without purging followed by bench-top solvents last. What is noticeable is that all the conversions are much lower than expected and this is thought to be due to both residual water, both in the starting reagents and also within the non-anhydrous solvents, restricting reactivity. The non-ideal order of addition of reagents also appears to be playing a role. The results do follow the expected trend of the more apolar solvents being preferable for the reaction with cyclohexane being the optimal solvent. Table 1.4.



Entry	Solvent	Percent Conversion by ^{1}H NMR
1	Heptane	7
2	Cyclohexane	8
3	Isopropylether	5
4	Dioxane	4
5	THF	7
6	Toluene	5
7	Acetonitrile	4
8	2-Propanol	3
9	Dichloroethane	3
10	Water	4

Table 1.4: Hafnocene with ammonium thiocyanate solvent screen

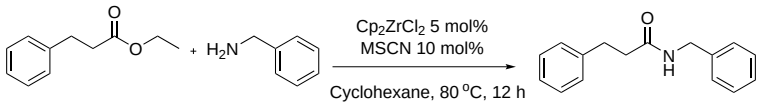
To ensure that these results were repeatable under ideal conditions the three solvents that gave the highest conversions were investigated along side the two best thiocyanate sources to determine how much effect each variable had under the anhydrous conditions. The results, summarised in Table 1.5, show that for hafnocene there is no large difference in the additive effects of sodium thiocyanate compared with ammonium thiocyanate and that for either cyclohexane is the preferable solvent followed by heptane.



	Percent Conversion by ^{1}H NMR	
Solvent	NH_4SCN	NaSCN
Heptane	40	31
Cyclohexane	49	47
THF	31	34

Table 1.5: Anhydrous solvent and thiocyanate check

Once the optimised conditions had been determined for the hafnocene catalysed aminolysis of ethyl hydrocinnamate with benzylamine, it was decided to insert zirconocene into the optimised conditions to determine if there was still a significant improvement with hafnium and whether it compensated enough for the extra cost relative to zirconium. The two reactions run side-by-side gave conversions of 61% for Cp_2HfCl_2 compared to 44% for Cp_2ZrCl_2 after three hours. Although a significant increase, it was decided, with hafnocene being approximately ten times the price (£14.05 per mmol compared with £1.43 for zirconocene, data from www.sigmaaldrich.co.uk on 11/02/14), that further reactions should be carried out with the zirconium analogue. It was also found that the zirconocene showed a greater reactivity when combined with the ammonia thiocyanate compared with the sodium thiocyanate and both compared well with the simply zirconocene catalysed reactions a summary of which is given in Table 1.6.

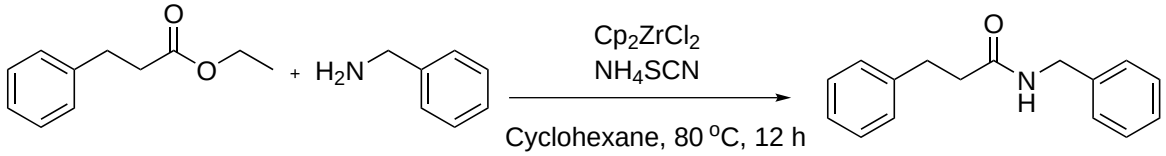


Entry	Thiocyanate	Percent Conversion by ^{1}H NMR
1	NaSCN	70
2	NH_4SCN	75
3	No thiocyanate	45
4	No cat. or additive	5

Table 1.6: Zirconocene thiocyanate comparisons

The ratio of catalyst and additive was investigated and it was found that increasing the concentration of either improved the conversions as one might expect. However increasing loadings above 5 mol% catalyst and 10 mol% thiocyanate additive was considered unnecessary. It was also noted that lower catalyst loadings did work without

too much loss of activity. These results are shown in Table 1.7 for the standard reaction run at 100 °C for five hours.

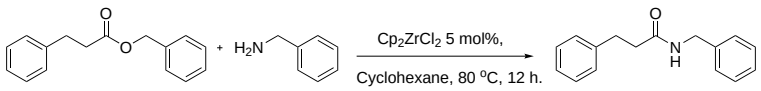


	Percent Conversion by ^{1}H NMR	
Mol% of Cp_2ZrCl_2	NH_4SCN 10 mol%	NH_4SCN 20 mol%
2.5	63	73
5	79	81
10	62	88

Table 1.7: Varying ratio of zirconocene and ammonium thiocyanate

It had been noticed that when dry milling of zirconocene and the metal-thiocyanates the reaction mixture remained a white colour, during argon purging at elevated temperatures, representative of the two white solids that were added. The addition of NH_4SCN, itself a bright white powder, did however lead to a yellow reaction mixture over the course of about ten minutes at 100 °C. It was thought this might be either the formation of an unexpected alternative catalyst or a form of reactive intermediate; either of which could be particularly susceptible to water or oxygen which would go some way to explaining the large effect that residual water appears to have, particularly when using the very hygroscopic ammonium thiocyanide.

The final stage of optimisation was to determine the best method for the drying of the thiocyanate, whilst methods including drying on a high vacuum with a heat gun did improve reactivity compared with the moist bench ammonium thiocyanate it was found that leaving a sample to dry overnight in an oven at 70-80 °C gave the best conversions. These conversions are reported in Table 1.8 and a clear difference can be seen by the addition of the dried ammonium thiocyanate additive to the zirconocene catalyst, as well as compared to the negligible conversions of the uncatalysed reaction. The optimised conditions for the acylation of a primary amine with an aliphatic unactivated ester is 10 mol% NH_4SCN with 5 mol% zirconocene dichloride catalyst, run in anhydrous cyclohexane for 12 hours at 80 °C.

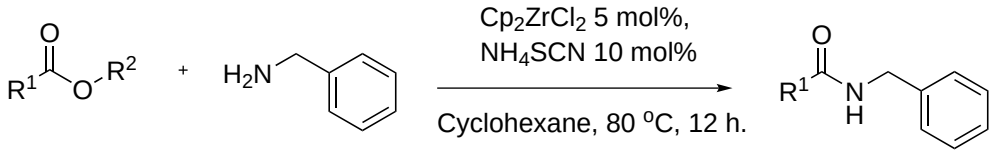


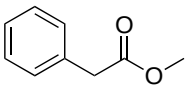
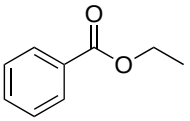
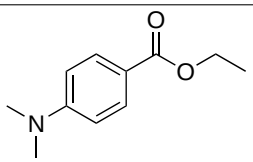
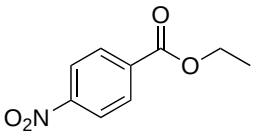
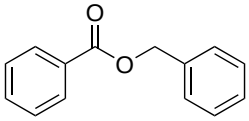
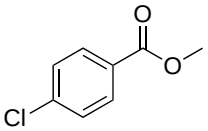
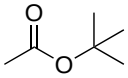
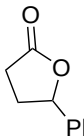
Catalyst	Percent Conversion by ^{1}H NMR
Cp_2ZrCl_2 + NH_4SCN	91
Just Cp_2ZrCl_2	45
No catalyst or additive	$<$1

Table 1.8: Optimised catalytic conditions, with and without additive

1.3.3 Range of esters

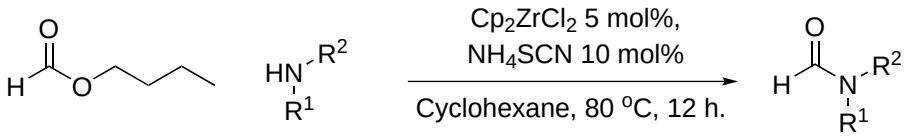
Table 1.9, showsthat both aliphatic and aromatic esters can be used to for amides with both electron donating and electron withdrawing substituents tolerated in the *para*-position. Sterically hindered esters such as the *tert*-butyl acetate showed some level of aminolysis but at a significantly lower conversion than the less hindered esters. An example of a lactone being converted into an amide is shown in a quantitative conversion with a good isolated yield.



Entry	Ester	Product ID	Temp. (°C)	Conversion	Isolated Yield
1		**1.1**	80	82%	72%
2		**1.2**	80	79%	76%
3		**1.3**	80	71%	56%
4		**1.4**	80	89%	89%
5		**1.5**	80	78%	76%
6		**1.6**	80	100%	58%
7		**1.7**	80	32%	31%
8		**1.8**	40	100%	88%

Reactions run on a 3 mmol scale in an argon atmosphere. Conversions as measured by ^{1}H NMR.

Table 1.9: Range of esters for aminolysis



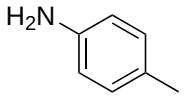
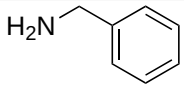
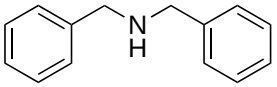
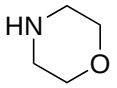
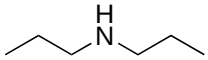
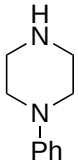
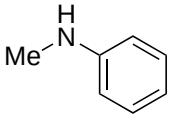
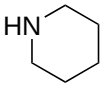
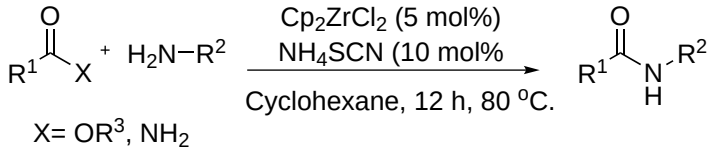
Entry	Amine	Product ID	Isolated Yield
1		**1.9**	92%
2		**1.10**	99%
3		**1.11**	99%
4		**1.12**	49%
5		**1.13**	60%
6		**1.14**	62%
7		**1.15**	95%
8		**1.16**	52%
9		**1.17**	86%

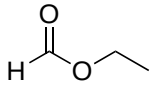
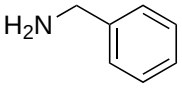
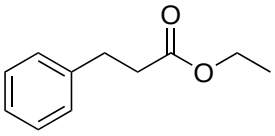
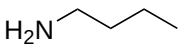
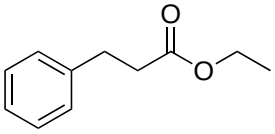
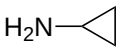
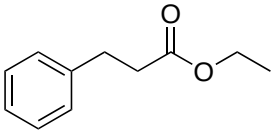
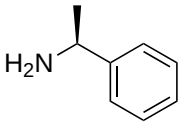
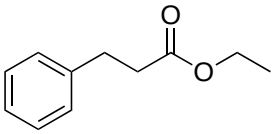
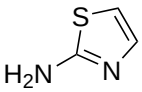
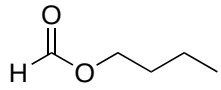
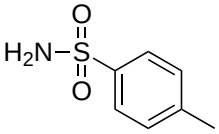
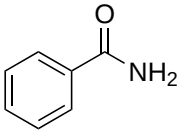
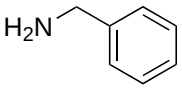
Table 1.10: *N*-Formylation of amines

What was surprising when looking at the formylation of secondary amines was that the conversion into amides mirrored a reverse in the trend one would expect to see when considering nucleophilicity. For example the sterically hindered and non-nucleophilic *N*-methyl aniline was isolated in 95% yield whereas the more nucleophilic amines morpholine and pyrrolidine showed much lower conversions. In order to determine whether the reaction was showing a surprising selectivity for poor nucleophiles or whether the good nucleophiles were poisoning the catalyst; a competition reaction was run contain-

ing one equivalent of morpholine and one equivalent of *N*-methylaniline. It was seen that there was far greater acylation of the morpholine than the anilinic nucleophile by a ratio of 5:1. This suggests that the simple cyclic amines are binding more strongly to the catalyst and poisoning it retarding the turnover of the catalytic cycle.

The final substrate screen was used to investigate the tolerance of the reaction to less common reactants as well as those that play important roles in biological systems and drug synthesis. The use of enantiomerically pure substrates was investigated to ensure high retention of the enantomeric purity and aromatic heterocycles were also investigated and shown to be acceptable substrates. Table 1.11.



Entry	Acylating Agent	Nucleophile	Product ID	% Yield
1			**1.18**	88 [a]
2			**1.19**	83
3			**1.20**	55
4			**1.21**	52
5			**1.22**	44
6				0
7				40 [b]

a) 24 h reaction run at 55 °C.
b) Conversion determined by ^{1}H NMR.

Table 1.11: Alternative Substrates

The use of alternative substrates was investigated to determine the limits of the methodology. The use of sulfonamides as nucleophiles was unsuccessful, this was attributed to their comparatively low nucleophilicity. Primary amides were investigated for transamidation and although successful the conversions were lower than alternative methodologies being investigated within the group. Carboxylic acids did not prove to

be convenient acyl donors and it is though that this might be due to the production of stoichiometric water upon acylation which could be damaging the catalyst.

1.3.4 Mechanism studies

There are four primary possible mechanisms for the increasing of catalytic activity upon the addition of ammonium thiocyanate which will be discussed. The first is the potential for the ammonium cation to be acting in some ways by binding to the carbonyl of the esters, withdrawing electron density and forming a more electron positive carbon centre for ready attack by the incoming amine. Although possible it is unlikely that this is the major catalytic pathway as other Lewis acids, such as scanduim triflate, did not show particularly good conversions under similar conditions nor would it explain the increase in catalytic efficacy when using tetrabutyl ammonium thiocyanate which is a poor Lewis acid.

An alternative mode of action could be envisioned involving a reaction of the ammonium thiocyanate with the zirconocene catalyst. This could occur by initial salt metathesis to give the zirconocene-thiocyanate and ammonium chloride. Ammonium chloride is known to decompose to hydrogen chloride and ammonia which could in turn potentially interact with the zirconium to yield a highly active zirconium amide species whilst generating thiocyanic acid. In order to determine if the decomposition of ammonium chloride was generating this reactive intermediate, dry, argon purged, zirconocene dichloride was milled with ammonium chloride at 80 °C for 16 h to ensure full reaction. This catalyst was then submitted to the reaction conditions to determine the conversion of ester into amide after 12 h at 80 °C with the data referenced against the conversions seen for the reactions recorded in Table 1.6. As the conversion after 12 h was only 24% with NH_4Cl as the additive it was clear that the reaction was hindered rather than expediated suggesting that this was not a likely catalytic route. Once again the resulting rise in catalytic activity on the addition of non-ammonium thiocyanates would also not be explained by this mechanism suggesting that it is highly unlikely indeed.

An alternative mode of activity could be the thiocyanate counterion acting as an acyl transfer agent in a mechanism, such as in the methodology hypothesised in Fig. 1.40, potentially with the ammonium counterion or the zirconocene dichloride promoting this in a Lewis acidic fashion. The resonance structures of the isothiocyanate allow for electric charge to be de-localised reducing nucleophilicity and the low $P_k a$ of the conjugate acids relative to alkoxides (*ca.* 1 vs 15) suggest that the thiocyanate would generally be the more stable anion.

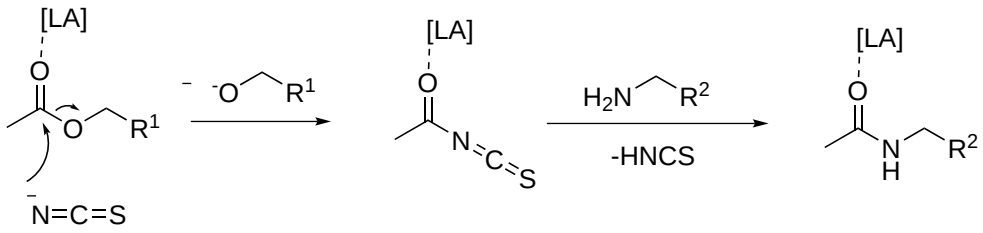
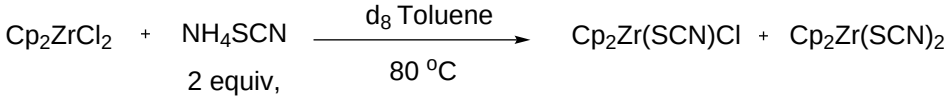


Figure 1.40: Thiocyanate acting as an acyl transfer agent

NMR experiments were conducted to determined if the acyl-thiocyanate was produced when stoichiometric quantities of sodium thiocyanate, zirconocene dichloride and an ester, in this case ethyl hydrocinnamate, were allowed to react together for 5 hours at 80 °C. Sodium thiocyanate was chosen to clarify the possible compounding of thiocyanate catalysed and ammonium ion catalysed reaction pathways. What was interesting was that no significant change was noted in the chemical shifts of either the ^{1}H NMR of the α-hydrogens on the ethoxide chain nor in the ^{13}C chemical shift of the carbonyl. The chemical shifts are given in Table 1.12 for selected peaks and one of the most conspicuous trends is the chemical shift of the Cp-rings attached to the zirconium on addition of the sodium thiocyanate.



Catalyst system	δ ^{1}H ester	δ ^{1}H Cp-rings [ratio]	δ ^{13}C Cp-rings
NH_4SCN & Cp_2ZrCl_2	3.90	5.94, 5.80, 5.66, [2.2:3.8:1]	116.2, 115.8, 115.3
Just Cp_2ZrCl_2	3.90	5.91	116.09
Neither catalyst	3.90	N/A	N/A

[nb] Selected chemical shifts of ethyl hydrocinnamate given in parts per million

Table 1.12: Chemical shifts for catalyst systems

This data suggests that it is the zirconium centre that is being affected rather than the substrates with the most likely situation being the salt metathesis of sodium chloride and formation of; zirconium bisthiocyanate, zirconium thiocyanate mono-chloride or more likely the isothiocyanate isomer of each considering the comparative hardness of the nitrogen atom with regards to sulfur ensuring a greater attraction to the hard d^0 zirconium centre. In order to ensure that these results were representative of general thiocyanate addition, ammonium thiocyanate in excess was added to zirconocene dichloride under an inert atmosphere with NMRs in toluene taken immediately after an

hour of dry milling at 100 °C and then after being stirred in toluene for five hours at 100 °C in solution. A similar pattern of peaks was seen in the spectra with a mixture of starting zirconocene dichloride and some mono-substituted zirconocene being seen after the initial dry milling and very little of the presumably bis-substituted product. After heating in solution for five hours most of the initial dichloride had been converted primarily into the mono-substituted product but with a significant amount of the bis-substituted product. The ratios of these cyclopentadienyl NMR integrations are given in Table 1.13.

	Percentage Integration of Cp^{1}H NMR signal		
Reaction conditions	Dichloride	Mono-substituted	Bis-substituted
Starting zirconocene	100	0	0
1 h dry milling	61	37	2
5 hours in solution	11	57	32

Table 1.13: Ammonium thiocyanate addition to zirconocene dichloride

One of the interesting points this raises is that the formation of zirconocene- isothiocyanates takes longer than might have been expected under the reaction conditions. This suggests that the large increases in catalytic activity, relative to zirconocene dichloride, seen in the experiments might be due to only fairly small fraction of the isothiocyanate species being formed. Attempts to form and isolate the unreported zirconocene di-isothiocyanate were made but separation from the starting zirconocene dichloride has so far been unsuccessful.

It is as yet unclear why the presence of a thiocyanate counterion on the zirconium has such a profound effect on the reactivity, as a stronger conjugate base than the chloride counterion that it is replacing it would be expected to adhere more strongly to the zirconium and resist dissociation. This is seen in the literature values for a range of thiocyanates with transition metals relative to metal chlorides where it registers a coordinating ability of 1.6 relative to chlorides 1.3, a triflate anion for comparison registering -0.4.[93] The size of the chloride anion compared to the nitrogen of the isothiocyanate might however be playing a role, freeing coordination space around the zirconium for binding of the esters. An alternative possibility could be that the resonance structures afforded by the thiocyanate fragment could act to attract the substrates through electrostatic effects although one might expect to see possible catalyst degradation through this pathway. The most likely of reasons for the increase in catalytic activity is due to the increase in solubility that occurs with counterion replacement. Zirconocene dichloride is very insoluble in cyclohexane and so even a slight increase in solubility will result in a much

greater quantity of zirconium in solution.

1.4 Summary

Zirconium and hafnium compounds have been shown to catalyse the aminolysis of esters rapidly for the production of amides with biscyclopentadienyl zirconium dichloride proving the most inexpensive highly active catalyst. The addition of a thiocyanate salt has been noted to increase the reactivity of zirconocene dichloride significantly as a catalyst for this reaction with ammonium thiocyanate proving to be the most favourable additive. It is of high importance to maintain anhydrous conditions, especially in the formation of the catalyst and anhydrous non-polar solvents, in particular cyclohexane, in an argon atmosphere have proved optimal.

Many secondary and tertiary amides have been formed in moderate to excellent yields with a wide range of functional groups showing tolerance to the methodology. Both aromatic and aliphatic esters could be utilised as starting substrates however it was noted that sterically hindered esters, such as tert-butyl acetate required significantly longer reaction times. Both aliphatic and anilinic amines could be used as nucleophiles however particularly nucleophilic amines were seen to poison the catalyst leading to lower yields.

Mechanistic studies have suggested that the formation of a zirconocene thiocyanate, either the mono- or bis-substituted, occurs significantly increasing the reactivity of the complex. Further work is required to precisely pin-point the mechanistic details of this advantage.

Chapter 2

Anhydride Activation

2.1 Introduction

The previous chapter has covered many of the main methods for acylations of nucleophiles, specifically the production of amides from amines, with the vast majority of the mechanisms being in many ways transferable. Of particular importance to this section is the Schotten-Baumann reaction, where an acid chloride is used as an acyl donor towards a protic nucleophile to yield the product and hydrogen chloride, as well as the use of organic compounds as acyl transfer reagents.

The Schotten-Baumann reaction has, as mentioned before, been used to form amides from amines since 1883. The acid chloride fragment can however be used to form a wide variety of other acylated products provided either an incoming substrate is nucleophilic enough or the acetyl has been activated with an additive or catalyst. There have been many methods reported for catalytic activation of the acyl fragment which fall under three main categories:

1. Nucleophilic activation - Displacement of the chloride with a better leaving group
2. Lewis acid activation - Withdrawal of electronic density from the carbonyl making it more electrophilic
3. Friedel-Crafts Acylation - Abstraction of the chloride to form a reactive acylium ion

Nucleophilic activation can either be through the addition of stoichiometric or ideally catalytic amounts of an additive. A large amount of the literature focuses on the use of non-protic *N*-heterocycles, such as DMAP, which attack the electrophilic carbonyl

to form the charged organo-acyl fragment with a chloride counterion.[94] Loss of this charged organic species is favourable so nucleophilic displacement occurs to regenerate the catalyst with the previously displaced chloride ion mopping up the superfluous proton from the nucleophile. Lewis acid activation by contrast either involves interaction of the carbonyl of the acid chloride with a variety of metals having been reported to catalyse the reaction in this method [95], [96] or through Lewis acid-Lewis base complexes. Friedel-Crafts acylations, first reported in 1877, are the final key mechanism for acylation with acid chlorides. Whilst initially reported for the acylation for aromatic compounds it has since found use in the acylation of a variety of carbon and heteroatom nucleophiles. A review by Pearson and Buehler showed many metal salts that could be used in very low catalyst loadings to achieve good levels of acylation albeit under high temperatures and harsh reaction conditions.[97]

Whilst all these methods have been well researched in recent years and each has its own merits there is one underlying problem for all of them, namely the production of stoichiometric HCl which either requires the addition of stoichiometric quantities of a base in order to neutralise the acid or for the reaction to be run in expensive mediating solvents which is not ideal. Additionally the production of acid chlorides generally involves the reaction of the parent carboxylic acid with primarily thionyl chloride or oxalyl chloride, both highly reactive, hazardous chemicals and involves the production of hazardous waste reducing the atom economy of the overall reaction. Subsequently a lot of research has investigated the use of acid anhydrides as substitutes for the acid chlorides; these are however intrinsically less reactive due to the increased donation from the conjoining oxygen atom into the carbonyls relative to chlorine. Whilst this decrease in reactivity can be beneficial, for example increased chemoselectivity and greater substrate stability, it does mean that the ability to acylate nucleophiles is correspondingly reduced. A lot of the literature has focussed predominantly on the first two mechanisms for activation of anhydrides, nucleophilic and Lewis acidic activation, as Friedel-Crafts type acylations tend to require a very good leaving group to produce the required stability for the highly activated acylium ion that is formed.

The literature in this section will mostly focus on the metal catalysed acylation of nucleophiles with acid-anhydrides in order to mirror the experimental work reported. The last two decades in particular have seen a large expansion in this area of research with catalytic methodologies using elements from all over the periodic table being reported. The literature mentioned herein focusses on the most salient and pioneering reports and the benefits and detriments of each route.

2.2 Metal Catalysed Anhydride Acylations

2.2.1 Early investigations

One of the earlier reports of metal catalysed acylations involves the use of a cobalt(II) chloride catalyst and shows noteworthy benefits compared with existing organocatalytic methodologies.[98] In the publication the authors show the chemoselective acylation of primary over secondary or tertiary alcohols and also the ability to acylate β-hydroxy esters and ketones without any determinable elimination as would be seen when utilising DMAP and its basic equivalents. A range of simple primary and secondary alcohols was shown to undergo acylation with acetic anhydride at either room temperature or 80 °C for the more challenging substrates in good to excellent isolated yields. A wide range of β-hydroxy esters and ketones was then acylated with acetic anhydride and the reactions were run in direct comparison with the standard literature DMAP conditions with the authors reporting higher yields of the desired β-acetate with none of the eliminated β-acetoxy carbonyl product in all cases. The authors have reported that analysis of the reaction mixture showed by-products which cannot be derived by typical ionic processes, this has led to the hypothesis that the cobalt(II) complex is acting as an electron transfer agent explaining the production of the diketone side products and postulating the mechanism for acylation shown in Fig. 2.1.

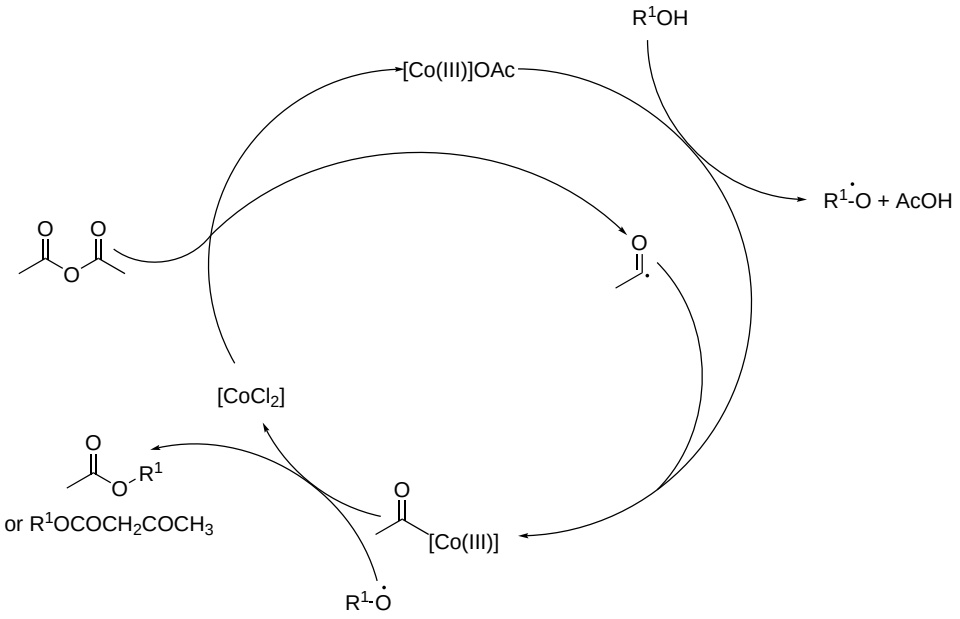


Figure 2.1: Mechanism of cobalt chloride catalysed acylation

An interesting report on the Friedel-Crafts acylation of aromatics with acid anhydrides was reported by Kobayashi *et al.* in 1995. A hafnium catalyst ($Hf(OTf)_4$) was utilised in a four molar solution of $LiClO_4$-$MeNO_2$ to acylate a range of electron neutral and electron rich benzene derivatives. It was reported that using the $LiClO_4$-$MeNO_2$ medium showed much increased catalytic activity for a range of Lewis acids with hafnium triflate proving the most effective catalyst investigated.[99] With the exception of benzene all the substrates tried were acylated in good to excellent yields at room temperature after six hours with the use of between 1-10 mol% catalyst. The authors had previously reported the use of lanthanide and scandium triflates as catalysts for Friedel-Crafts acylations and although they also showed a marked increase in the $LiClO_4$-$MeNO_2$ media they were not seen to be as effective as the hafnium salt.

There have also been reports moving away from the conventional use of homogeneous Lewis acids for Friedel-Crafts acylations due in part to the cost of the frequently non-recyclable catalysts and also the requirement for purification particularly for high quality goods such as drugs. The use of heterogeneous catalytic methodologies can impart some benefits and the work of Chaudary and co-workers explores the potential use of ion-exchange clays for the acylation of electron rich aromatics.[100] Zeolites based on solid acids, derived from montmorillonite which were impregnated with salts or had the metal ions exchanged, were investigated for the acylation of 2-methoxynaphthalene with acetic and propionic anhydride. It was seen that the Fe^{3+} montmorillonite was the optimal catalyst investigated and that it withstood multiple uses without a significant

loss of activity. Nitrobenzene was found to be the most favourable solvent and whilst the reaction yields went up when the reaction was run above 80 °C, the selectivity for acylation in the 1-position decreased with acylation in the thermodynamically favourable 6-position increasing. A major benefit to this method is that although reaction temperatures are higher and reaction times longer than previously reported the catalyst only contained 2.1% Fe^{3+} loadings and could be simply recycled, washed and reused.[100]

2.2.2 Lewis acidic triflate salts

Scandium triflate was reported as an effective catalyst for the acylation of a range of alcohols under particularly mild conditions and was seen to out perform both DMAP and the basic tributylphosphine catalysts that were the contemporary standards. The authors also showed the ability to produce carboxylic esters utilising the Mukaiyama method of forming a mixed anhydride *in situ*. This was shown to work most efficiently for aromatic carboxylic acids and less for aliphatic versions with para-nitrobenzoic acid proving a good coupling agent. The ability to form medium to large ring lactones from ω-hydroxy carboxylic acids selectively was also demonstrated with excellent yields being seen for rings of 7-17 atoms with very little diolide seen. It was noted that both secondary and tertiary alcohols could also be acylated using this methodology and an interesting selectivity was seen when the acylation reactions were run with one equivalent of both benzyl alcohol and 3-phenyl propanol. The acylation occurred with almost complete selectivity for the aliphatic alcohol rather than the benzylic nucleophile, this is the opposite selectivity compared with that shown by the DMAP catalysed acylations.[101]

An alternative mode of acylation was describes by Kalita and co-workers where simple anhydrides such as acetic anhydride were again used as acylating agents; however in this report the nucleophiles investigated were aldehydes. This led to the production of 1,1-acylals catalysed by molecular iodine and could even tolerate the presence of tertiary alcohols. The reactions were run at ambient temperature for between half an hour and 2 hours to produce the diacetates in excellent yields negating the need for strong acids such as sulfuric or methanesulfonic acid that had previously been reported for this reaction.[102]

Following the use of $Sc(OTf)_3$ reported by Yamamoto and colleagues there have been a plethora of methodologies using triflate catalysts to acylate alcohols. One such report published in 1998 utilises trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a highly active catalyst usually only requiring between 0.5 and 2 mol% catalyst loadings although for benzoylations the reactions did require up to 30 mol% catalyst for acyla-

tions in practical time frames. For very simple alcohols such as 2-octanol, acetylation could be seen to occur within 30 s without disruption of stereocentres when enantiomerically pure alcohols were used. Direct comparisons against scandium triflate were made and the authors assert that it is a more powerful catalyst and was able to tolerate even very acid sensitive groups.[103]

A variety of indium salts, but in particular indium trifluoromethanesulfonate, have been reported as very good catalysts for the Friedel-Crafts acylation of a range of aromatic compounds and other organic molecules. Whilst $InCl_3$ and $In(ClO_4)_3$ also showed catalytic activity for acylation of anisole with acetic anhydride they did not perform as well as the $In(OTf)_3$ when coupled with a lithium perchlorate additive. The additive is believed to act to form a reactive cation species in combination with the acyl donor and was shown not to catalyse the standard reaction in the absence on indium. The reaction, which was shown to catalyse only the acylation of electron rich aromatics in good yields, demonstrated that alternative acyl sources could be activated using indium salts, including isopropenyl acetate the product of which after acylation enolizes rapidly to produce acetone. Whilst these were shown to be good acylating agents of mono alcohols it was shown for 1,2-diols that a competing reaction was also occurring by which the acetone by-product was undergoing a ketalisation process to produce an acetal protected diol, the mechanism for which was also promoted by the indium catalyst, Fig. 2.2. When acetone was used instead of the acylating reagent the reaction could be used to generate high yields of the acetal with indium triflate again proving to be the best catalyst.[104]

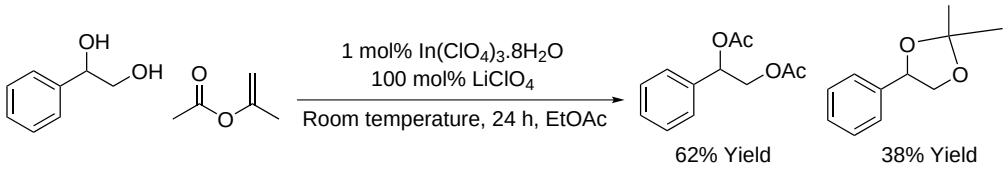


Figure 2.2: Indium catalysed diol protection

Whilst highlighting the versatility of the triflate counterion it is worth noting that a range of f-block triflates have been reported over the past decade as catalysts for acylations. One of the earliest reports utilising cerium triflate was published in 2003 by Procopio and co-workers.[105] As a highly active catalyst cerium triflate was shown to work with catalyst loadings of generally 1 mol% for a wide range of alcohol substrates producing the esters in excellent yields although only acylations were reported. Whilst some tertiary alcohols were shown to acylate in good yields, particularly sterically hindered ones did not show any acylation and similarly the acylation of some electronically de-

activated alcohols required the use of catalyst loadings of up to 10 mol%. Interesting selectivities were reported for the acetylation of 2-(para-hydroxyphenyl)ethanol at varying temperatures; at -10 °C only acylation on the aliphatic alcohol was seen whereas at -30 °C only acetylation on the phenol was detected. It is thought that this is due to the cerium acting as a Lewis acid at the higher temperatures allowing the more nucleophilic alcohol to attack whereas at the lower temperatures it is thought that the overriding effect is of the triflate counterion acting as a base, removing the more acidic phenol proton allowing for the aromatic alcohol acylation.[105] The use of erbium triflate as an acylation catalyst was later reported, detailing a much greater substrate scope and importantly the potential for the use of other anhydrides for acylation, including for tertiary alcohols and electron poor phenolic alcohols. One of the benefits of the erbium methodology is the relative cheapness of the catalyst compared with $Sc(OTf)_3$ and $Ce(OTf)_3$ and the ability to recover and reuse the catalyst.[106] All of the lanthanide triflates reported so far have required stringently anhydrous conditions to reduce degradation of the catalyst; however a report from Reddy and co-workers describes the use of gadolinium triflate for the acylation of a broad scope of alcohols and some amines with very low catalyst loadings without the need for strictly anhydrous solvents. It is believed, due to ^{13}C labelling studies, that the reaction proceeds through the formation of the mixed anhydride, acetic triflic anhydride, which is then attacked by the nucleophile generating the acetylated alcohol and regenerating the $Gd(OTf)_3$ catalyst as shown in Fig. 2.3.[107]

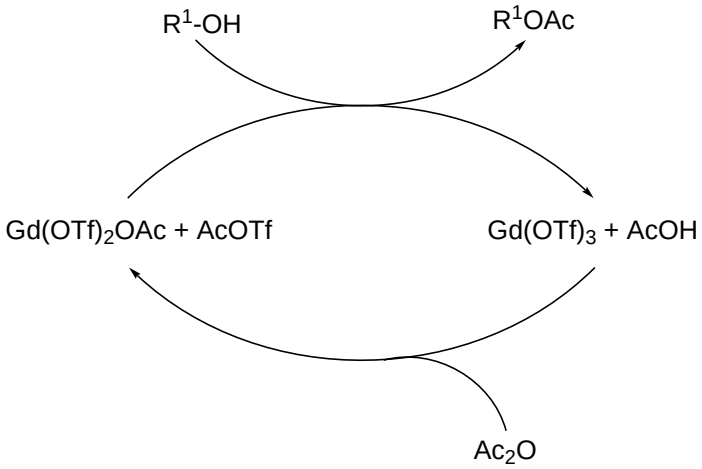


Figure 2.3: Mechanism of $Gd(OTf)_3$ catalysed acetylation

Attempts to make more industrially relevant catalysts have been looked at and the use of a recyclable $Yb(OTf)_3$ catalyst was demonstrated by Barrett and was shown to be able to acylate alcohols after repeated uses with acetic acid as the acyl donor. Com-

paratively longer reaction times or higher temperatures were required however due to the decreased reactivity of the acetic acid relative to the anhydride.[108] A variety of lanthanide triflates was investigated by Scheeren for the catalytic acylation of an alcohol containing natural products. This included investigating lutetium triflate which gave the product in quantitative conversion within three hours when two equivalents of acetic anhydride were used.[109] Alternatives to the use of rare earth triflates have been investigated over recent years in a general trend towards more readily available metals. A report of the use of copper triflate for acetylation of various alcohols, at room temperature for primary alcohols and at 65 °C for secondary alcohols, resulted in good to excellent yields. The mechanism is thought to proceed through a similar mixed anhydride method to the gadolinium catalytic system Fig. 2.3. Some selectivity was seen for the mono-acylation of primary alcohols over secondary alcohols in the case of diols although there was significant diacetylation in most cases.[110] The main group compound bismuth trifluoromethanesulfonate has also been described as a powerful acylation catalyst and showed the propensity to acylate with less susceptible reagents such as benzoic or pivalic anhydride. Surprisingly for such a powerful catalyst it was very mild and did not interfere with acid sensitive substrates such as THP-protected alcohols as well as allowing for base sensitive groups such as esters. The practical benefits of using an air and moisture stable catalyst such as $Bi(OTf)_3$ was complemented by its ability to acylate even sterically hindered alcohols without dehydration at catalyst loadings as low as 0.5 mol%.[111] The use of metal triflates and similar counterions extends to the s-block where both lithium triflate and magnesium bistrifluoromethanesulfonimide have been reported as acylation catalysts. The magnesium report showed that alcohols could be acylated with benzoyl and pivoyl groups as well as acetate groups in good yields even for tertiary and phenolic alcohols. These magnesium catalysed reactions were run in the absence of solvent with a large excess of the alcohol using catalyst loadings of 1 mol%.[112] The lithium publication by contrast utilises the considerably cheaper lighter triflate counterion albeit in higher catalyst loadings (20-30 mol%) and is reported acetylating a wide range of aliphatic and aromatic alcohols in excellent yields. It has also been proven to form the 1,1-diacetate from aldehydes at room temperature in a mild fashion with complete selectivity of aldehyde protection over ketones for a range of aliphatic and aromatic aldehydes although no chemoselectivity was seen between the two.[113]

The literature contains a plethora of publications about the use of many of the metal triflates as acylation catalysts; the triflate anion however is an expensive fragment, sometimes more so that the metal it is in combination with. Recent investigations have therefore looked into the use of alternative salts both of lanthanide metal salts and also

others from around the periodic table. In some cases the same metals have been shown to catalyse the acylation reactions with a more available counterion; examples of this such as indium chloride or ytterbium chloride can show similar reactivities to their triflate analogues albeit occasionally under very different conditions. In the $InCl_3$ example the use of stoichiometric $Li(ClO_4)$ was not required when the reaction was run neat although a larger excess of acetic anhydride was required for sterically hindered alcohols and there were no analogous reports of Friedel-Crafts acylation.[114] The ytterbium chloride paper showed some very interesting selectivities for the mono-acylation of symmetrical diols. Both cyclic and acyclic diols were shown to mono-acylate for both syn- and anti-diols in very good selectivities; the use of less active active acylating reagents, such as benzoic or Boc anhydride, could also be used. When $Yb(OTf)_3$, a more reactive catalyst, was investigated for the reaction with acetic anhydride, there was no notable selectivity for the mono-acetylation and considerable amounts of side reaction involving opening up and polymerization of the THF solvent. The use of the less reactive benzoic anhydride however proved ideal with this more electron poor catalyst. The mechanism is not yet clear but is believed to include both the diol and the anhydride bound to the lanthanide centre, enabling an intramolecular transfer of the acyl group. This results in a 7-membered chelate that is rapidly replaced by a more stable 5-membered diol chelate. This mechanism explains the experimental observation that C_2 symmetrical diols react more rapidly than meso-diols as chelation for meso-diols involves eclipsing of the two R^1-groups raising the energy of the system. Fig. 2.4.

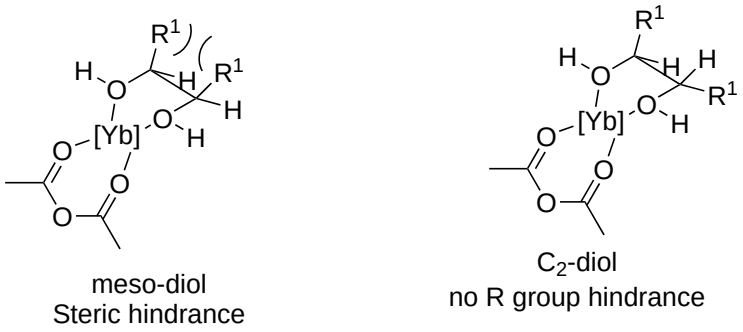


Figure 2.4: Ytterbium catalysed mono-acylation

2.2.3 Alternative catalysts

One important recent area of investigation has focussed on the use of molecular iodine as an efficient catalyst for solvent free acylations with a variety of acylating agents. An early report by Phukan described the acetylation of a range of nucleophiles with only a

very slight excess of acetic anhydride in excellent yields including for some substrates, such as ones containing internal and terminal alkenes, which might have been expected to interact with the iodine.[115] A similar report by Saikia and co-workers also looked at the acylation of alcohols catalysed by molecular iodine however the acylating agent of choice in this case was vinyl acetate. Both primary and secondary alcohols could be acylated by this mechanism with preference shown for electron rich alcohols however the methodology did not stretch to acylating tertiary or phenolic alcohols. It is believed that the mechanism proceeds by activation of both the carbonyl and double bond of the vinyl acetate making the substrate more susceptible to nucleophilic attack as shown in Fig. 2.5. This produces the vinyl alkoxide which upon protonation can tautomerise to give acetaldehyde, a non-acidic waste product in contrast to the use of acid chlorides or anhydrides meaning that the reaction medium remains neutral.[116]

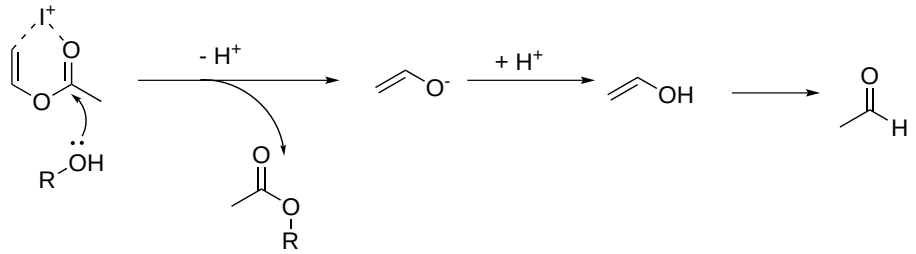


Figure 2.5: Iodide catalysed acetylation with vinyl acetate

Some of the most efficient catalysts that do not employ expensive counterions are the simple s- and d-block halides such as $RuCl_3$[117], $MgBr_2$[118], and $ZnCl_2$.[119] The ruthenium chloride methodology was explored for a wide range of nucleophiles including; alcohols, phenols, thiols and amines and it showed great tolerance to the sorts of acid sensitive groups that were incompatible with some of the metal triflate catalysts. The magnesium bromide methodology by comparison did not report on the acylation of any substrates other than alcohols although the scope of ester formation was considerable with even electron poor tertiary alcohols showing moderate conversions without elimination. The reaction tolerated most functionalities that might chelate the magnesium such as nitro-groups with an exception being drawn for 1-phenylethane-1,2-diol which showed no acylation under the standard conditions.

Some important work has been done by Reddy and co-workers into the acylation of more challenging nucleophiles than alcohols, specifically in the zinc chloride catalysed *N*-acylation of sulfonamides. Acylated sulfonamides are important moieties in both drug designs and particularly agrochemicals thus an industrially viable method for catalytic acylations is desired. The reported methodology requires low catalyst loadings (3 mol%)

to provide a range of acetylated sulfonamides in very rapid reaction times in the absence of a solvent; the use of alternative anhydrides was also investigated with a wide range proving applicable including sterically hindered examples such as pivalic anhydride. The authors also demonstrated the ability to utilise $ZnCl_2$ as a catalyst for acylations using carboxylic acids as the acyl donor requiring slightly higher catalyst loadings but still relatively short reaction times.[119]

In a more recent publication alternative metal catalysts have been investigated for the *N*-acylation of sulfonamides and the authors have focused on the hydrogen sulfate salts of aluminium and zinc for both heterogeneous and solvent free acylations.[120] Both primary and secondary sulfonamides showed the ability to acylate in high yields in most cases in under an hour at room temperature and the methodology even encompassed the previously unreported acylation of bis-sulfonamides although higher reaction temperatures were required. The mechanism reported by the authors suggests that an acylium ion might be formed when acylating with the carboxylic acid anhydride whereas when the catalyst system is used in conjunction with acid chlorides it is thought that the catalyst acts as a simple acid which explains why the anhydrides react quicker of the two.

As has been reported there are many different catalysts for the acylation of simple nucleophiles primarily using acid chlorides and carboxylic acid anhydrides although there are reports of similar alternative acyl donors that have their own benefits and disadvantages. Many of these catalytic methods involve rare earth or scarce metals and frequently require a trifluoromethanesulfonate counterion which is expensive and reduces the atom economy of the overall reaction.Whilst some recent papers have described elegant methodologies for the catalytic acylation of a range of nucleophiles other than alcohols it still remains a comparatively under explored area of interest.

2.3 Group Interest into Acylations

Our group started being interested in catalytic acylations when the addition of DBN was demonstrated to be able to catalyse the acylation of pyrroles and indoles using many different acid chlorides. It was proposed that the mechanism was proceeding through nucleophilic organic catalysis with the DBN adding to the carbonyl of the acid chloride and displacing the chloride anion to form an *N*-acyl intermediate. This was proven to be the case by a mixture of kinetic isotope effect reactions as well as by mass spectrometry, IR and NMR spectroscopy. It was seen that after replacing the chloride anion with a tetrafluoroborate anion, crystals could be grown that showed the anhydride out of plane with the DBN increasing the electrophilicity of the carbonyl as it is not stabilised by

resonance, hence allowing for its catalytic nature. Further investigations were conducted to isolate the stable ionic intermediates formed from the acylation of DBN and to use these salts as acylating agents for a wide range of nucleophiles including; primary and secondary amines, alcohols,[121] primary sulfonamides, *N*-alkylsulfonamides [122] as well as indoles and pyrroles when in the presence of catalytic DBN.[123]

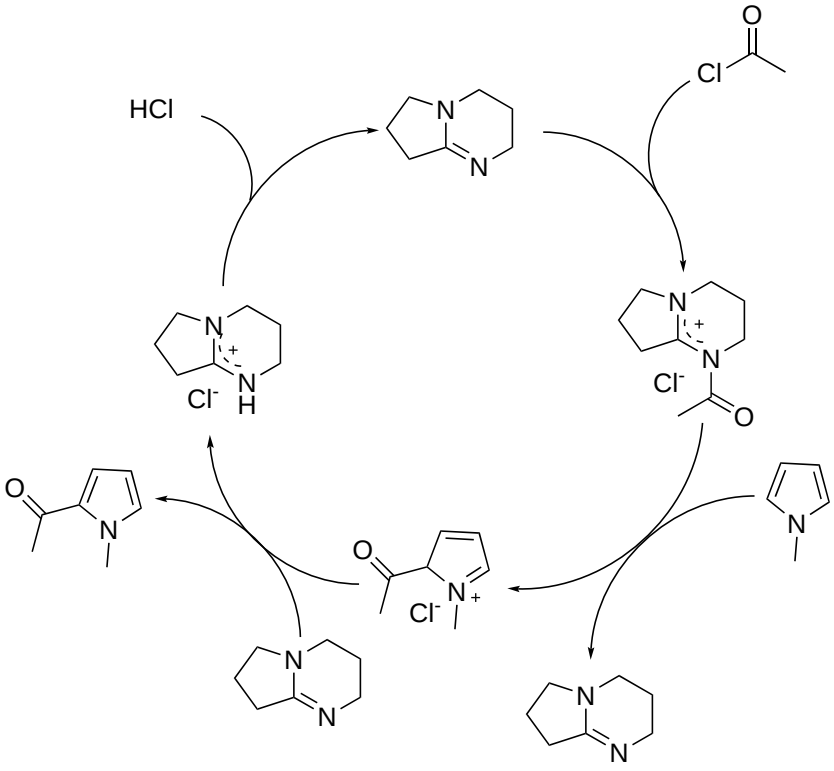


Figure 2.6: Mechanism for the DBN catalysed acylation of heterocycles

Attempts to increase the reactivity of this reaction were made as a significant background reaction occurred under the optimised conditions with a variety of additives investigated. Of this initial screen lithium bromide was determined to be the best additive when used in a stoichiometric quantity increasing the catalytic conversion from 12% with just the catalyst to a quantitative conversion within half an hour. In order to determine which of the methods of activation the DBN-LiBr catalyst additive system was following, Fig 2.7, the reaction temperatures were lowered and a screen of similar lithium salts were investigated. With lithium iodide still showing a much greater reactivity the suggestion is that the salts' anion was key to the catalytic activity. This consideration was enforced by the lack of reactivity of $LiClO_4$ which is a source of lithium without a nucleophilic counterion. Whilst trying to determine the synergistic activity of the DBN and the LiI it was noted with surprise that whilst acting as a good additive

in conjunction with the DBN catalyst the activity of stoichiometric LiI alone was even greater, with conversions of 64% compared with 54% with the DBN. A screen of lithium halide salts alongside DBN showed that the catalytic activity of the systems matched the expected trend with respect to the corresponding acid halide, i.e. iodide> bromide> chloride.

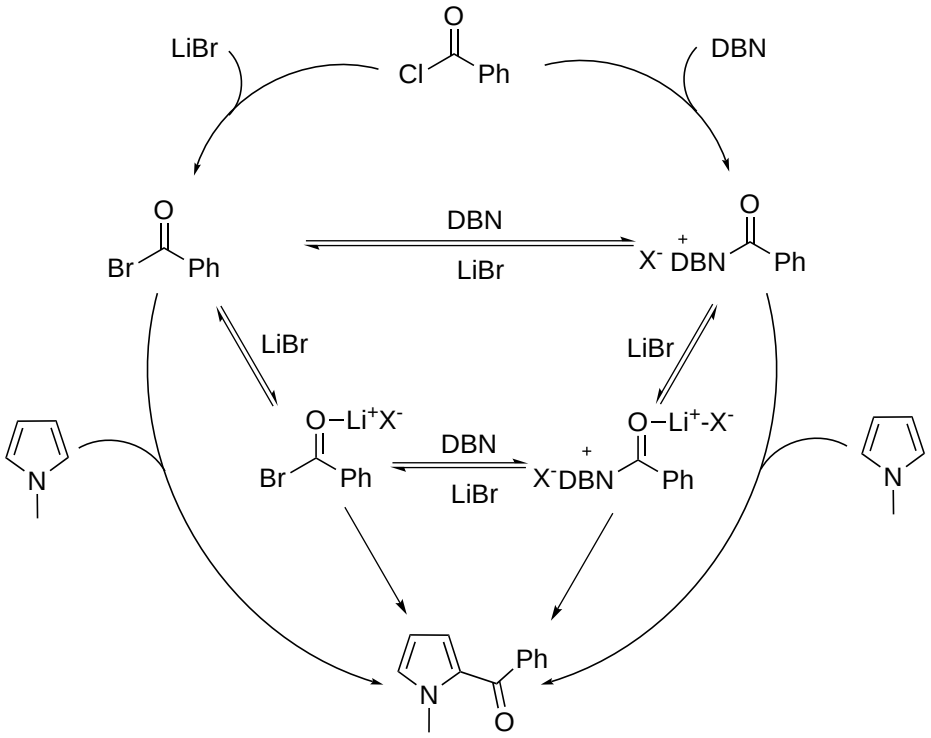


Figure 2.7: Potential roles of DBN and LiBr in heterocycle acylation

The formation of an acid halide and in the optimum case an acid iodide is key to understanding some of the trends in reactivity with the iodide as the best nucleophile the formation of the acid iodide should be the most rapid of the series and the increased conversions mirror this. Alternative iodide sources were investigated but none of the ones tried showed comparable levels of efficacy as lithium iodide. It was also seen that under these conditions neither super-stoichiometric or sub-stoichiometric quantities of the additive improved the reaction. As might be expected for a reaction involving the formation of a reactive intermediate, the solvent used had a large effect on the efficacy of the reaction. Of the solvents investigated ethyl acetate proved to be optimum providing conversions of 80% in an hour at 80 °C however the addition of 4 Å molecular sieves (4 Å MS) brought the conversions up to quantitative levels through removal of water rather than through heterogeneous catalytic methods. The optimised reaction conditions were taken forward to test the robustness and compatibility of the acylation reactions with a

range of acid chlorides being reported in mostly excellent conversions with the exception of the sterically hindered pivalic chloride.

Mechanistic aspects to the reaction were investigated with the possibility of the reaction proceeding through a solely Lewis acid catalysed mechanism discounted. This is due to the fact that the alternative lithium salts investigated were significantly less effective for the reaction; also the use of the coordinating ethyl acetate was optimal for the reaction whereas it would be expected to hinder such a process proceeding *via* this mechanism. Spectroscopic data supporting the formation of an acid iodide intermediate supported the hypothesis that this is a key intermediate in the reaction. This was determined by the addition of one equivalent of LiI to the acid chloride and exposing it to the standard reaction conditions for one hour prior to the addition of a nucleophile. A ^{13}C NMR spectrum taken at this point showed the formation of a significant amount of acid iodide with little starting acid chloride, removal of the lithium chloride by filter cannulation of the solution into a fresh reaction vessel followed by the addition of *N*-methyl pyrrole showed that the benzoyl iodide could produce the acylated product in quantitative yields under the normal reaction conditions.

This work had shown the potential for group(I) iodides to act as stoichiometric additives for the activation of acid chlorides to acid iodides; enabling them to act as much better acylating agents for the Friedel-Crafts acylation of protected pyrroles. Whilst this was an interesting revelation it would be desirable if the methodology could be adapted to allow for catalytic acylations. This work was carried forward by another colleague who decided to investigate the catalytic acylation of *para*-toluenesulfonamide as the reaction for optimisation with benzoyl chloride as the acylating agent of choice. An initial screen of group(I) iodides as catalysts showed that sodium and potassium iodide were the two most effective catalysts with conversions of 78% and 69% respectively when 20 mol% of the catalyst was used. The next stage of optimization, after determining that acetonitrile was the best solvent, was to ensure that the acylation of this more reactive substrate also required an iodide rather than simple Lewis acid catalysis. This was demonstrated by a screen of group one halides with the iodides proving the best catalysts and in particular potassium iodide which saw a conversion maxima at catalyst loadings of 60 mol%. To confirm that this reaction was also proceeding through an acid iodide formed *in situ,* hourly NMR spectra were taken with the addition of 60 mol% potassium iodide at 70 °C over a period of 24 h. This showed the formation of the acid iodide over time up to an equilibrium point of approximately 20% relative to the remaining benzoyl chloride which as there was a greater quantity of iodide added to the reaction mixture suggests that a dynamic equilibrium had been reached. Interestingly it was

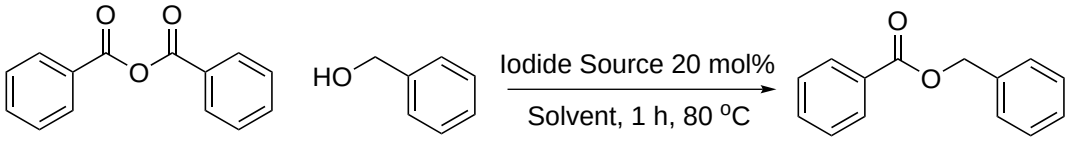
noted by the author that the addition of tetrabutylammonium iodide did not form any acid iodide; this could either be due to the greater dissociation of potassium salt relative to the ammonium salt, allowing for an increased concentration of iodide, or evidence for synergistic effects of the potassium counterion. A comparison between the reactivities of acid chloride and acid iodide was made by the addition of a comparative quantity of nucleophile compared to acid iodide (20 mol% as based on the ^{13}C NMR). It was seen that the acid iodide reacted instantaneously in preference to the acid chloride but returned to its initial approximately 20 mol% equilibrium after a few hours. This result implies that the rate limiting step is the formation of the acid iodide which could be expected as, although iodide is a good nucleophile for S_{N^2} attack at sp^3 carbon centres, it is a comparatively poor nucleophile for the hard sp^2 carbonyl centre. Whilst this goes some way to explaining the equilibrium of acid chloride to acid iodide seen, it is not automatically clear why the less electronegative iodide appears to be the better acid halide for acylating. The authors have attributed this to the increased polarizability of the iodide and the poor overlap of the electrons on the iodide with the π^* of the carbonyl meaning that it remains more electrophilic than the corresponding acid chloride.[124]

2.3.1 Summary

As s-block iodide salts have been demonstrated to be good catalysts for the acylation of nucleophiles with acid chlorides *via* the process of forming an acid iodide intermediate, it was decided to investigate whether less activated acylating agents, namely carboxylic acid anhydrides, could be activated in a similar fashion. As the carboxylate conjugate base of an anhydride has a significantly higher pKa than the chloride displaced from an acid chloride it is unclear as to whether this mechanism of nucleophilic iodide addition will extend to these substrates. It will be desirable to find a suitable iodide based catalyst to catalyse a range of nucleophilic additions. s-Block metals in particular are inexpensive and readily available and will avoid the necessity of rare earth metals or triflate counterions. The additional benefit of anhydride acylations is that they may, due to their inherent lack of activity compared with acid chlorides and iodides, be able to impart some additional chemoselectivity. The ability to acylate challenging nucleophiles without the production of stoichiometric amounts of hazardous waste will be investigated along with mechanistic aspects of the reaction in order to determine the pathway by which the reaction is proceeding.

2.4 Optimisation

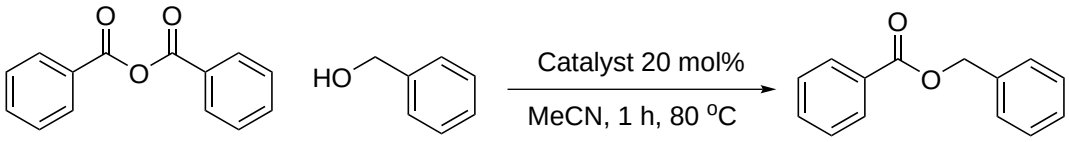
Initial work was conducted to determine which iodide salt would be optimal for the benzoylation of benzyl alcohol which was used as the standard substrate for all of the optimization reactions. Group(I) metals were the first to be investigated as well as with ammonium iodide and tertbutyl ammonium iodide which shows very little acid character. From this screen, the results of which are shown in Table 2.1, it was evident that lithium iodide showed the best conversions overall in both solvents. The inability of *tetra*-butylammonium iodide to catalyse the reaction suggests that it is unlikely to be primarily, if at all, proceeding through a nucleophilic iodide pathway and suggests that Lewis acidity is likely to be playing a role.



Catalyst	Conversion in MeCN (%)	Conversion in EtOAc (%)
LiI	5	26
NaI	2	10
KI	1	7
RbI	3	7
CsI	5	14
NH_4I	2	4
$^{t}Bu_4NI$	0	0
No catalyst	1	6

Table 2.1: Group (I) iodide screen

Alternative salts of s-block metals and other well known Lewis acids were investigated to determine which weres the most effective catalysts under the reaction conditions and to compare their efficacy with previously reported catalysts, the results of which are displayed in Table 2.2.3. The reaction time was increased slightly to two hours in most cases to give a wider range of results and acetonitrile was chosen as the solvent as there was the least background reaction with which to compete. It was clear that the magnesium salts were amongst the most effective, this is not surprising as they have a very similar radius to the lithium salts allowing for similar modes of coordination to the substrate. As they are in the 2^{+} state however they will have an increased charge density allowing for greater electron withdrawal from the anhydride. Of the catalysts tried, magnesium iodide was the most effective for the benzoylation of benzyl alcohol in acetonitrile and so was taken on for further optimisation.

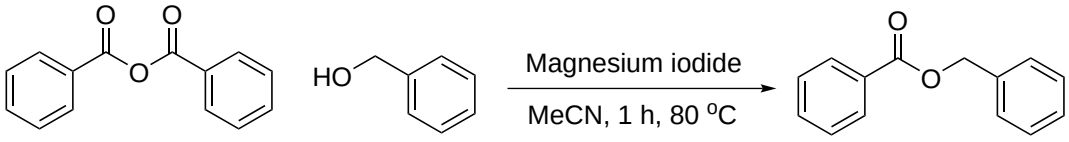


Lewis acid catalyst	Conversion to ester (%)[a]
$Mg(NO_3)_2$	79
$Mg(OAc)_2$	42
$MgCl_2$	89
MgI_2	97[b]
$Cu(OAc)_2$	7
$Cu(NO_3)_2$	72
$ZnCl_2$	14
$Zn(NO_3)_2$	59
Cp_2ZrCl_2	24
No catalyst	1

a) Conversion measured by ^{1}H NMR
b) Reaction time 30 mins

Table 2.2: Lewis acid catalyst screen

Solvent screens were conducted and it was found that for magnesium iodide acetonitrile at reflux was the optimal solvent with regards to high conversions with clean reaction products. Ethereal solvents also showed good potential especially when higher temperatures were required with dioxane proving one of the better solvents for use at 100 °C, above the boiling point of acetonitrile. A comparison of catalyst loadings run in THF showed that for the benzoylation of benzyl alcohol, catalyst loadings of below 5 mol% resulted in a large decrease in catalyst activity, this could be attributed to moisture reacting with the catalyst; the effect of which would be magnified at low catalyst loadings. Table 2.3.



MgI_2 loadings	Conversion (%)
5 mol%	61
1 mol%	6
0.5 mol%	5

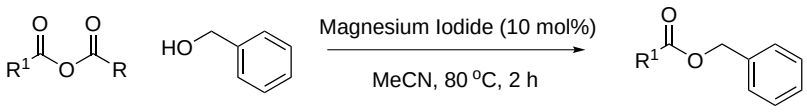
Table 2.3: Catalyst loadings in THF

The optimised conditions for the benzoylation of simple alcohols were determined to be as follows; 5-10 mol% magnesium iodide at one molar concentration in acetonitrile at 80 °C and these conditions were taken forward to acylate a range of simple nucleophiles with a selection of anhydrides.

2.5 Results and Discussion

2.5.1 Simple nucleophiles

Taking benzyl alcohol a selection of commercially available anhydrides was investigated to determine the substrate scope of the reaction with regards to the electrophile. The results are displayed in Table 2.4.



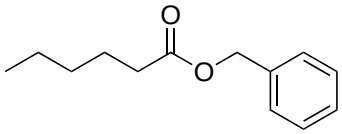
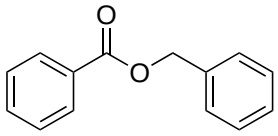
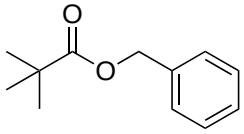
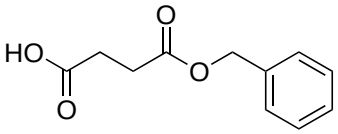
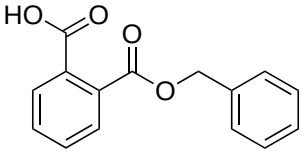
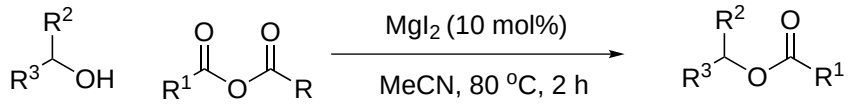
Entry	Ester formed	Product ID	Isolated yield
1		**2.1**	86%
2		**2.2**	99%
3		**2.3**	95%
4		**2.4**	54%
5		**2.5**	60%

Table 2.4: Benzyl esters formed from anhydrides

Boc anhydride was investigated but found to be unsuccessfully as an electrophile for the alcohol as a reaction appeared to occur, as judged by effervescence upon addition of the Boc anhydride to a solution containing magnesium iodide, prior to addition of a nucleophile with no nucleophile carbonylation seen and appearance of degradation of the Boc_2O. A range of the more common anhydrides were then successfully shown to acylate more challenging alcohols, the results of which are reported in Table 2.5.



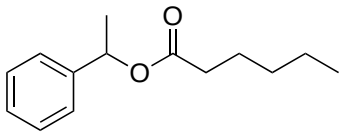
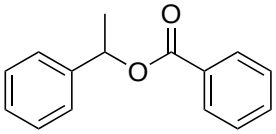
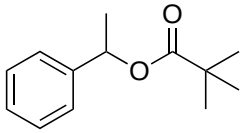
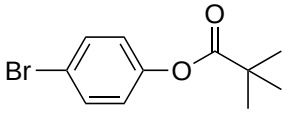
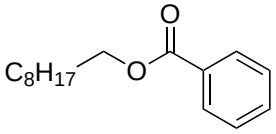
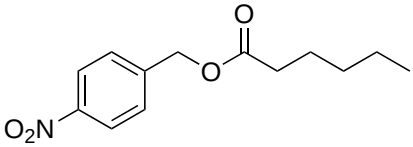
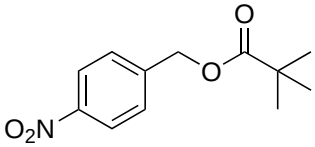
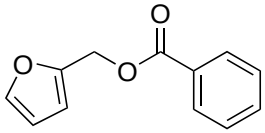
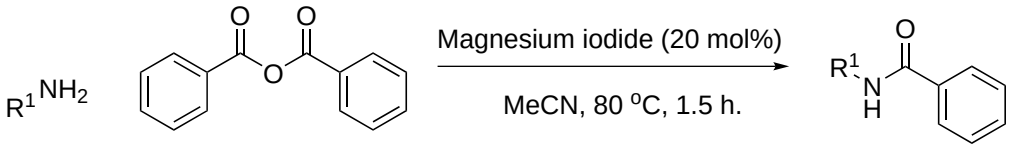
Entry	Ester Formed	Product ID	Isolated Yield
1		**2.6**	88%
2		**2.7**	55%
3		**2.8**	90%
4		**2.9**	79%
5		**2.10**	97%
6		**2.11**	100%
7		**2.12**	99%
8		**2.13**	49%

Table 2.5: Range of ester formation catalysed by magnesium iodide

Of the substrates investigated it was clear that both electron rich and electron poor alcohols are successfully acylated by this methodology. Tolerance was seen for both halogens as well as nitro groups which could hinder the reaction by chelating the magnesium

ion. There were low isolated yields seen for the acylation of furanol which is attributed to decomposition of the sensitive starting material in the reaction mixture rather than an inherent lack of nucleophilicity. To prove the generality of the reaction a handful of aliphatic and aromatic amines were benzoylated in high yields as displayed in Table 2.6.



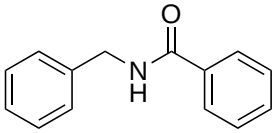
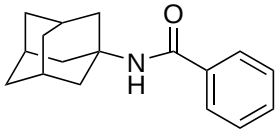
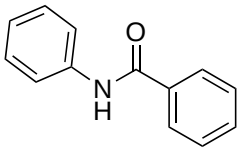
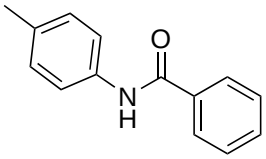
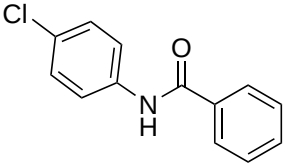
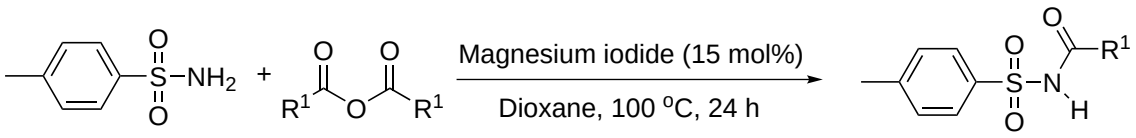
Entry	Amide formed	Product ID	Isolated yield
1		**2.14**	91%
2		**2.15**	81%
3		**2.16**	88%
4		**2.17**	81%
5		**2.18**	80%

Table 2.6: Amine acylation

2.5.2 Sulfonamides

One of the key intentions of this project was to investigate the acylation of more challenging nucleophiles. In particular; nucleophiles that are intrinsically less nucleophilic than alcohols, nucleophiles that are sterically challenging and also some carbon nucleophiles that have not been investigated for acylation by anhydrides. Sulfonamides are a good example of less nucleophilic substrates that play a key role in many

pharmaceuticals and agrochemicals when in their acylated form. Optimisation for the acylation of sulfonamides showed that higher temperatures and longer reaction times were required, thus dioxane was chosen as the solvent and the reactions were allowed to react for 24 hours at 100 °C. Initial reactions were run using *para*-toluenesulfonamide to investigate the range of anhydrides that could be used as acylating agents and as can be seen in Table 2.7, there was a range of both aliphatic and benzoic anhydrides that could be used to produce the esters in mostly good isolated yields.



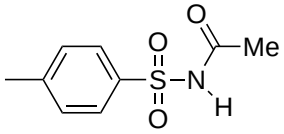
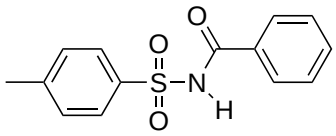
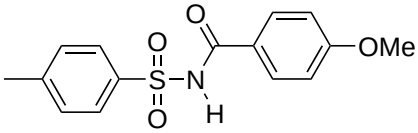
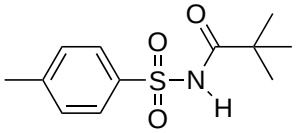
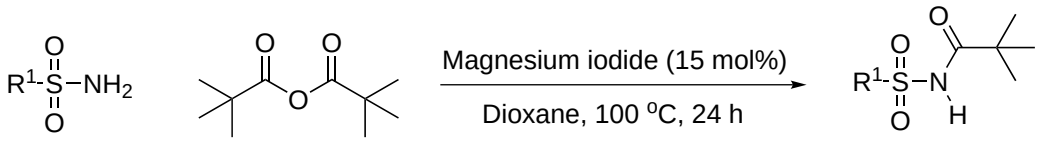
Entry	Sulfonamide	Product ID	Isolated Yield
1		**2.19**	83%
2		**2.20**	55%
3		**2.21**	65%
4		**2.22**	83%

Table 2.7: Acylation of *p*-toluenesulfonamide

The next step was to determine which sulfonamides were active under the reaction conditions. For this reaction the electron rich sterically hindered pivalic anhydride was chosen as the acylating agent and again the reactions required comparatively high catalyst loadings and relatively long reaction times but in all cases the pivoylated sulfonamides were returned in good yields, Table 2.8. Both electron rich and electron poor sulfonamides were tolerated as were the presence of aryl halides and esters.



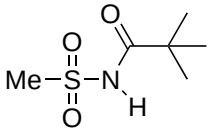
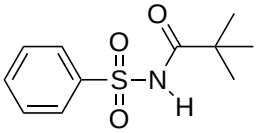
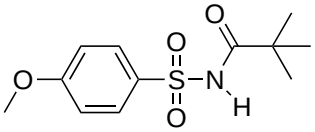
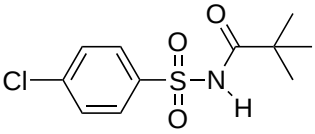
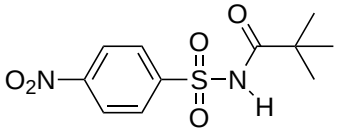
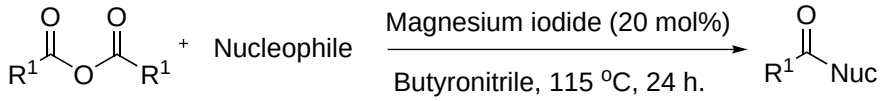
Entry	Sulfonamide	Product ID	Isolated yield
1		2.23	73%
2		2.24	85%
3		2.25	78%
4		2.26	83%
5		2.27	44%

Table 2.8: Pivoylation of a range of sulfonamides

2.5.3 Challenging nucleophiles

Magnesium iodide proved a useful catalyst in the acylation of simple nucleophiles such as alcohols and amines, as well as being able to extend the methodology to acylate less reactive nucleophiles such as sulfonamides. It was therefore decided to investigate some other, previously unreported, acylations with anhydrides as well as acylations that had been reported as difficult. One of the most challenging substrates to acylate was 2,6-*tert*-butoxide-4-hydroxytoluene (BHT) which is a particularly poor nucleophile as the electrons on the oxygen atom are withdrawn into the aromatic ring and the considerable steric bulk of the two o*rtho*-*tert*-butyl groups repel the electrophiles with which you would wish it to react. There is some precedent for the acetylation of BHT using acetic anhydride with primarily lanthanide triflates and heterogeneous catalysts however the acylation of BHT with alternative anhydrides is a very understudied area. As can be

seen in Table 2.9, magnesium iodide does catalyse the reaction well for the sterically non-bulky electrophiles such as acetic and hexanoic anhydride, entries 1 and 2, which reacted to give excellent conversions. The use however of bulkier anhydrides such as benzoic and pivalic anhydride, entries 3 and 4, severely decreased the conversions recorded. A similarly under reported acylation is that of amides to produce imides, this is mostly due to the initial stability and poor nucleophilicity of the amide. As steric concerns are less important compared with BHT acylation there were similar levels of acylation seen with pivalic anhydride relative to acetic anhydride, entries 6 and 5 respectively. The increased reactivity of the pivalic anhydride suggests there might potentially be a slight change in reaction mechanism.



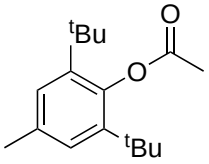
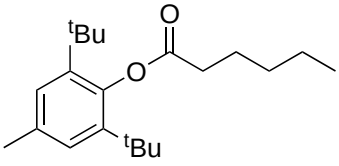
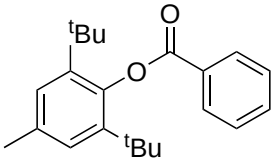
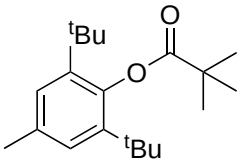
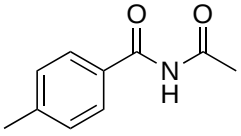
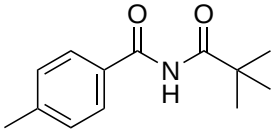
Entry	Acylated compound	Product ID	Conversion (Isolated)
1			97%
2			87%
3			14%
4			4%
5			48%
6		**2.28**	43 (36)%

Table 2.9: Challenging heteroatom reactions

The final section of challenging substrates that were looked at were carbon nucleophiles and in particular the acylation of electron rich heterocycles. Initial attempts at acylating anisole, a common Friedel-Crafts substrate, under the initial conditions of 10 mol% MgI_2 in acetonitrile at reflux were unsuccessful and so acylation on pyrroles and indoles were investigated instead. Both proved susceptible to acylations with a range of acid anhydrides with the acylation of 1-methylpyrrole being particularly interesting; as the ratio of acylation in the 2 or 3 position depended on the steric bulk of the acylating

agent. Acetic anhydride showed preference for the 2-position as expected whilst pivalic anhydride acylated predominantly in the 3-postion. Neither of these reactions could be optimised to form a single isomer unfortunately and so investigations moved on to the acylation of 1-methylindole. Whilst this substrate is intrinsically less reactive, due to the electron withdrawing effects of the aromatic ring, it would be expected to show significant selectivity for the 3-position of the indole in all cases. It would seem that the use of the magnesium iodide catalyst in a lot of the indole acylation reactions causes the degradation of the starting material or the product to form intractable mixtures that were unresolvable by chromatography. The exception to this was when pivalic anhydride was utilised as the acylating agent; in this case the 3-trimethylacetyl-1-methylindole product [Product ID: **2.29**] was isolated by recrystallization in an excellent yield. Fig. 2.8. Attempts were made to acylate alternative heterocycles but imidazoles proved to be too electron poor and the use of alternative protecting groups on pyrroles and indoles, such as sulfonates which should increase stability for isolation, proved to deactivate the substrates too much to allow them to react.

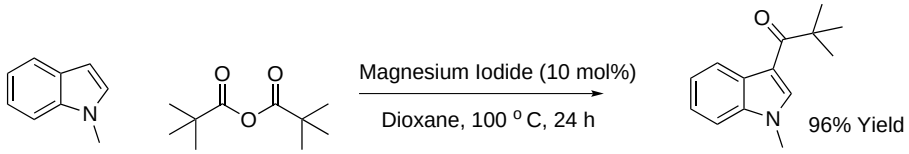


Figure 2.8: Indole acylation

2.6 Mechanistic Studies

There are three primary routes that the magnesium iodide catalyst may be activating the acid anhydride substrates to form a more electrophilic carbonyl for attack and these are illustrated in Fig. 2.9. Route A demonstrates the classical Friedel-Crafts formation of an acylium ion which as a relatively unstable ion will readily undergo attack by a protic nucleophile. Route B shows the catalytic activation of the acid anhydride to the acid iodide in a mechanism analogous to that reported for the activation of acid chlorides by a member of our group. The acid iodide with its poorer overlap in orbital symmetry of the electron pairs on the iodide with the π*- of the carbonyl means that there is less stabilisation of the positive charge experienced by the carbon atom making it more electrophilic. Route C shows the binding of the carbonyls of the anhydrides to the Lewis acidic magnesium ion, pulling electron density from the substrate and lowering the energy of its lowest unoccupied molecular orbital (LUMO), thus enhancing its ability to react with nucleophiles.

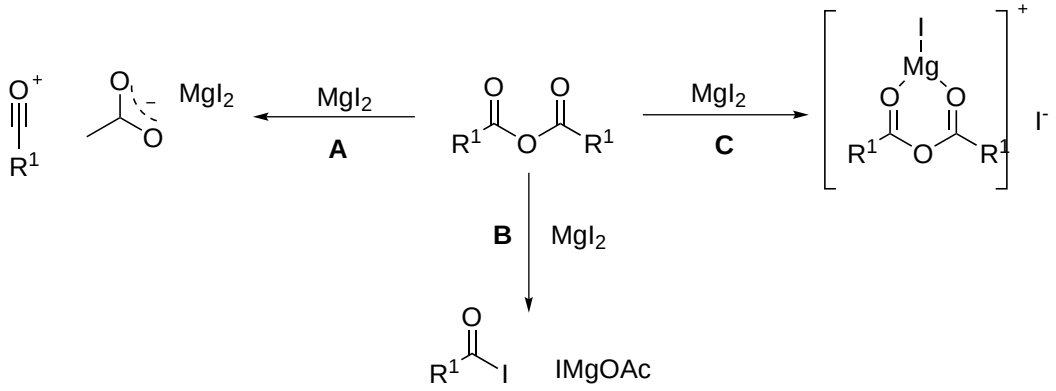


Figure 2.9: Potential mechanisms of MgI_2 anhydride activation

The first area of investigation was to determine if the magnesium ion was integral to the reaction or whether it was purely activated by the iodide. Although none of the reactions shown in Fig. 2.9 would automatically be discounted, as all could be expediated with the presence of a Lewis acid, the removal of such would give some clues as to the role of each ion. Crown ethers have long been known to sequester metal cations with some selectivity in ring size being seen dependant on the cationic radius of the metal ion. It was decided to investigate a range of crown ethers, alongside 10 mol% of the magnesium catalyst, in the optimised benzoylation of benzyl alcohol reaction. Table 2.10 clearly demonstrates that all the crown ethers investigated hinder the reaction with 15-Crown 5 showing the highest affinity for the magnesium. This demonstrates that the magnesium is playing a key role and supports the results determined in the optimisation section which showed that the non-Lewis acid source of iodide, tetra-butylammonium iodide, was not effective for the reaction.

Crown ether (20 mol%)	Conversion (1 h)
12-Crown 4	18%
15-Crown 5	1%
18-Crown 6	17%
No crown ether	91%

Table 2.10: Results of magnesium sequestration

The next stage in investigating the reaction mechanism was to undertake a series of NMR experiments to determine whether or not certain key intermediates are formed in the absence of a nucleophile. Route B predicts the formation of an acid iodide which has a signature chemical shift at 159 ppm for the carbonyl of a benzoyl iodide.[124] This could be expected to be in a form of dynamic equilibrium with the acid anhydride. In order to try to form this intermediate for detection, stoichiometric magnesium iodide

was added to the benzoic anhydride in deuterated acetonitrile and heated at close to reflux whilst detecting for the formation of the acid iodide as shown in Fig. 2.10. No discernible peak was seen to suggest any formation of an acid iodide; this was not unexpected considering the high pKa of carboxylate relative to the analogous chloride. In the acid chloride example the acid iodide was formed in an approximately 1:4 ratio with respect to the acid chloride under the optimum conditions. A significantly poorer leaving group will decrease the ability to form this equilibrium despite iodide's inherent nucleophilicity which suggests that another mechanism is in action.

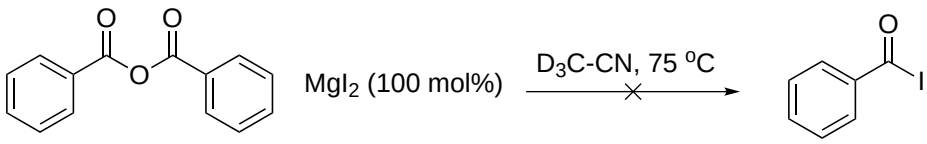


Figure 2.10: NMR experiment to detect the formation of acid iodide.

It is thought that the process, at least in most cases, is not proceeding through the formation of an acylium cation similar to that seen in the Friedel-Crafts reaction. This is supported by the lack of evidence of an acylium ion in the ^{13}C NMR, reported to appear at 150.3 ppm, in the earlier reaction searching for the formation of the acid iodide.[124] Other evidence dismissing the formation of acylium ions is the inability to acylate substrates such as anisole under normal reaction conditions. This would be expected to occur, at least to some degree, if the reaction was proceeding by a Friedel-Crafts mechanism. One exception to this might be occurring in the acylation of some particularly poor nucleophiles, such as amides, which require very high temperatures and high catalyst loadings in polar aprotic solvents. The harsher conditions might be enough to form the reactive intermediate and this could go some way to explaining the acylating ability of pivalic anhydride relative to acetic anhydride under these conditions. Attempts under these very harsh polar conditions were again made to acylate the carbon nucleophile anisole with pivalic anhydride to try trap out any acylium ions formed but no conversion to the 1-(4-methoxy)-2,2-dimethyl-1-propanone was seen.

2.7 Summary

Previous work within the group had shown the ability to use alkali metal iodides as both stoichiometric and catalytic additives for the acylation of a variety of substrates with acid chlorides. This was shown by the use of NMR techniques to proceed through the formation of an acid iodide intermediate which reacts more rapidly with the incoming nucleophile. This characteristic is attributed to the increased polarity of the iodide and

the decrease in orbital overlap of the iodide's electrons with the carbonyl leaving a less filled antibonding orbital for S_{N^2} attack.

S-block metal iodides have been shown within this body of work to act as good catalysts for the activation of acid anhydrides for the acylation of a variety of simple as well as challenging nucleophiles being reported using a range of aliphatic and aromatic acid anhydrides. Magnesium iodide was determined to be the most effective catalyst and worked most efficiently when used in polar solvents such as acetonitrile. The mechanism was proposed by a combination of NMR studies and sequestration reactions to proceed *via* a Lewis acid catalysed mechanism in contrast with the acid iodide mechanism previously reported. Acylations of alcohols were shown for the most part to be facile however the use of electronically poor, sterically hindered alcohols such as BHT required harsher conditions and although simple aliphatic anhydrides could be used as acylating agents the more bulky acylating agents showed low conversions.

Chapter 3

Amine Borane Reductions & Reductive Coupling

3.1 Introduction

3.1.1 Transfer hydrogenation and hydrogen borrowing within the group

The Williams group has long been interested in the process of transfer-hydrogenation and hydrogen-borrowing techniques with a very wide variety of metal additives and catalysts having been investigated for a range of different reactions. One of the earlier reports from the group involved the addition of a carbon nucleophile, namely methyl malonitrile, to vinyl alcohols. Whilst this nucleophilic attack would not normally occur, the use of a Meerwein-Pondorff-Verely (MPV) aluminium catalyst in conjunction with a catalytic substrate, for reversible hydrogen acception/donation, showed that the alkene could be activated towards nucleophilic attack by temporary conversion of the vinyl alcohol into a conjugated ketone. This ketone once having undergone conjugate addition can then be reduced back to the alcoholic form it began in, as shown in Fig. 3.1, to produce the alkylated product in up to 90% isolated yield, the theoretical maximum yield under these conditions.[125]

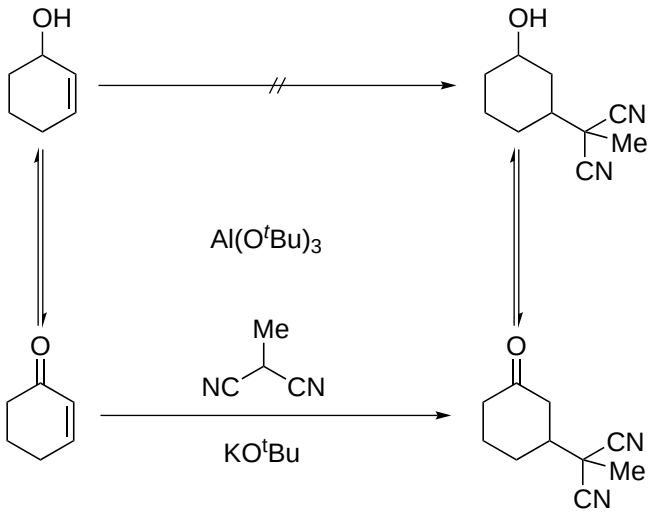


Figure 3.1: Aluminium alkoxide catalysed electronic activation

This work was followed up by again looking at the activation of alcohols but with the intention of performing an indirect Wittig olefination upon the substrate; this can, upon the return of the borrowed hydrogen, be reduced to give the alkylated product with the formation of a carbon carbon single bond. Initially this work was investigated with an iridium complex which demonstrated good selectivities and high reactivities when used under relatively harsh reaction conditions, good isolated yields seen in most cases. One of the main exceptions to this was seen when secondary alcohols were used as a build up of the ketone, produced by oxidation of the alcohol, occurred with less proceeding through to the olefin or alkylated products.[126] This methodology was greatly improved by the use of a ruthenium NHC complex that had previously been reported to demonstrate C-H activation of a CH_3 of an aromatic arm of the NHC which was reversible on the addition of hydrogen to form the ruthenium dihydride. When a sacrificial catalytic amount of vinyltrimethylsilane was used, so as to complete the initial dehydrogenation of the catalyst, the methodology was shown to enable the indirect Wittig activation of alcohols to form a range of saturated ester products from the starting ester ylids. Excellent yields were reported at 80 °C in 24 h rather than the 150 °C previously reported for the iridium complex. The key step of the reversible dehydration of the ruthenium NHC complex and C-H activation of the ligand is shown in Fig. 3.2.[127]

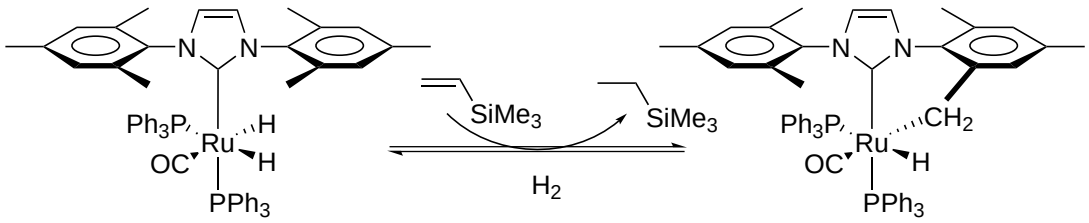


Figure 3.2: Reversible dehydrogenation of a Ru catalyst for indirect Wittig olefination

Attempts were made to extend this methodology to the production of enantiomerically enriched reduced Wittig products. Initial investigations focussed on the stereoselective transfer hydrogenation of the olefin, which would be formed by the Wittig reaction. A range of platinum group metal catalysts and chiral ligands were investigated whilst using an excess of isopropyl alcohol as the sacrificial hydrogen source. From the initial screens it was determined that 5 mol% of $[Ir(cod)Cl]_2$ with a BINAP ligand in 5.5 mol% loadings provided the greatest conversions whilst maintaining high enantioselectivity with the alkene reductions. With the use of toluene as the solvent, instead of IPA, the asymmetric indirect Wittig reaction of benzyl alcohol with a phosphonium ylide was reported with 68% conversion with an enantiomeric excess of 87%.[128]

The use of temporarily borrowing hydrogen for activation of substrates and returning the hydrogen to give the modified product can be very atom economical and generally produces clean reactions. At times however the reactions do not proceed to completion due to the equilibrium of products and hydrogen source, which is essential for the catalytic cycle. A similar effect can be seen for transfer hydrogenation reactions unless a considerable excess of one of the substrates is used which is particularly the case for hard to reduce substrates. Considering this, the group has investigated the use of alternative hydrogen sources which shift the point of equilibrium so that once they have either accepted or donated hydrogens the likelihood of the reverse reaction occurring is thermodynamically very much reduced.

There are two key methods through which this can be achieved, the first is by using a hydrogen donor that has a significant variation in oxidation potential between the hydrogenated and non-hydrogenated form relative to the substrate. For example the reduction of 1-phenylethanol with acetone will require several equivalents of acetone to produce high conversions as the oxidation potentials are quite similar. The use of formaldehyde by comparison, which as an aldehyde converting to a primary alcohol is less destabilizing than the ketone to secondary alcohol conversion, would require fewer equivalents to produce comparative conversions.

The alternative is to trap out the product of the oxidation or reduction so that the reverse reaction is not possible. There are two primary methods for this; tautomerisation

of the product to a much more stable compound or by cyclisation. One example of the use of this second technique within the group was reported for the reduction of a range of aldehydes and ketones using a ruthenium catalyst and investigating a selection of diols. The choice of diols meant that each could act as as an equivalent source of two molecules of H_2 whilst forming the stable lactone as the driving force of the reaction as seen in Fig. 3.3. This methodology was implemented in the enantioselective reduction of certain ketones with the Noyori catalyst rather than the common use of an excess of isopropyl alcohol with good conversions and high enantiomeric excesses reported.[129]

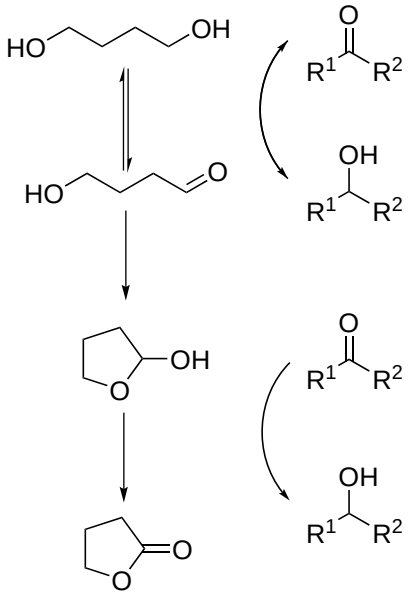


Figure 3.3: Irreversible hydrogen donation and lactone formation from 1,4-butanediol

In an attempt to find a more atom economical route for the formation of allylic esters from alcohols through borrowing hydrogen methodology, the use of malonate half-esters was investigated with the use of a simple commercially available ruthenium catalyst, $Ru(PPh_3)_3Cl_2$. The benefit of this method over the previously reported indirect Wittig reactions is the lack of waste triphenylphosphine oxide which is highly atom uneconomical and challenging to remove. The following decarboxylative Konevenagel method, by comparison, only produces the waste products of water and carbon dioxide. The use of monoethyl malonate, to alkylate a range of electron poor and electron rich benzyl alcohols, was described although electron poor and aliphatic alcohols required higher catalyst loadings of 5 mol%. In order to overcome the slight loss of H_2 gas that occurred, causing the formation of a mix of predominantly the alkylated product as expected as well as an impurity of the non-reduced alkene intermediate, 20 mol% IPA was added. This was sufficient to compensate for any loss without affecting the overall

reaction.

The work mentioned above is just a small example of some of the initial successes from within the group in the field of transfer hydrogenation and hydrogen borrowing and it presents a succinct overview of some of the key mechanisms and patterns of reactivity. The majority of the work with the exception of the MPV-O reaction has focussed on the use of late transition group metals, in particular ruthenium and iridium which is a pattern seen throughout a lot of the literature on transfer hydrogenation. Also mentioned above is the use of reversible hydrogen donors and acceptors with particular application to hydrogen borrowing, or transfer hydrogenation when used in excess, along with a description of the contemporary use of irreversible hydrogen donors, used stoichiometrically to drive reactions in a more atom economical fashion.

3.2 Amine borane decoupling

Although not directly intended as a source of hydrogen for either transfer hydrogenation or hydrogen borrowing, work within the group at the time was investigating alternative ruthenium complexes. Particular focus was given to the cationic $[Ru(xanthos)(PPh_3)H]^+$ $[BAr^f{}_4]^-$, [Ru(dppf)(PPh_3)HCl] and the NHC complex [Ru(dppf)(ICy)HCl]and their reactions with amine boranes. A lot of the interest in investigating amine boranes centres around the incredibly high ratios of hydrogen that can be released per molecule which affords a light weight, dense energy source. This can then be used readily in hydrogen fuel cells to create an efficient clean alternative to the internal combustion engine. Initial results with the neutral 18 electron phosphine species did not show significant dehydrogenation of amine boranes as measured by ^{11}B NMR ($<$10% conversion after 72 h). Attempts to replace the PPh_3 with a variety of NHCs was made with only the ICy (1,3-Bis(1-cyclohexyl)imidazolium) and IAd (1,3-Bis(1-adamantyl)imidazolium) mono-substituted compounds being isolatable. These two compounds showed agostic stabilising through the α-positions on one of the cyclohexyl or adamantyl rings causing a distorted geometry around the ruthenium. The ICy substituted compound proved far more adept at the dehydrogenation of amine boranes with almost quantitative dehydrogenation in 0.25 h rather than the 72 h previously required. The IAd compound by comparison showed very little improvement compared with the phosphine substituted ruthenium catalyst. In the case of the ICy catalyst it is believed by the authors that the NHC may be playing a key role in the dehydrogenation by accepting a proton from the amine borane. They have postulated that the time lag seen at the start of the reaction is due to either dissociation of the agostic interaction or loss of an ancillary ligand rather than proceeding through a heterogeneous pathway that can display similar reaction characteristics.[130]

3.2.1 Early transition metal catalysed amine borane decoupling.

A lot of the pioneering work in this field was conducted by Manners and co-workers who described the homogeneous dehydrocoupling of amine-borane adducts by titanocene. Whilst previous work had shown that the use of dimethyltitanocene was ineffectual for dehydrocoupling of dimethylamine borane (DMAB) at room temperature, even after 160 h, they reported that the addition of 2 equivalents of BuLi to titanocene dichloride formed a catalyst that could dehydrocouple DMAB quantitatively within 4 hours even at low catalyst loadings of 2 mol%. The precise nature of the catalyst and mechanism of operation is not precisely known although the addition of the BuLi is believed to form a Cp_2TiBu_2 species which slowly forms a titanium(II) species that is catalytically active. The catalyst was shown not to be heterogeneous by both the filtration of the solution which did not significantly decrease the rate of reaction and also by the addition of mercury, which is known to adsorb on to heterogeneous catalysts, or to form amalgams and inhibit their activity which was not seen in this case.[131]

This work, exploring group(IV) sandwich compounds, was continued by Pun *et al.* when they investigated a wide range of isolatable functionalised titanocene and zirconocene based catalysts. It was hypothesised by the authors that producing isolatable catalysts would help elucidate the mechanism of catalysis being followed and it was expected that the use of metallocenes, where the cyclopentadienyl is robustly bound to the metal, would decreased the possibility of colloid formation. In their initial screen of metallocenes for the dehydrogenation of dimethylamine borane in benzene it was found that steric hindrance around the cyclopentadienyl ring decreased the reactivity whilst small electron withdrawing groups improve reactivity. Zirconocene catalysts proved to be poor catalysts in comparison with the titanium based catalysts. The optimum catalyst, shown in Fig. 3.4, was found to be the disilylated cyclopentadiene bridged titanium dimer. The authors postulated a mechanism for the dehydrogenation of DMAB, Fig. 3.4. This was supported by deuterium studies whereby the reaction was run in a D_2 atmosphere and deuterium was seen to be incorporated on the boron of the starting amine borane and potentially also on to the amine suggesting interesting reversibility in the reaction. Investigations into the comparative lack of reactivity seen for the zirconium compounds were made and it was noticed that, along with a considerable amount of zirconocene borohydride with the corresponding loss of dimethylamine, there were some occurrences where the aromatic ligands attached to the zirconium were themselves reduced. This both decreased the yield of hydrogen and affected the catalyst.[132]

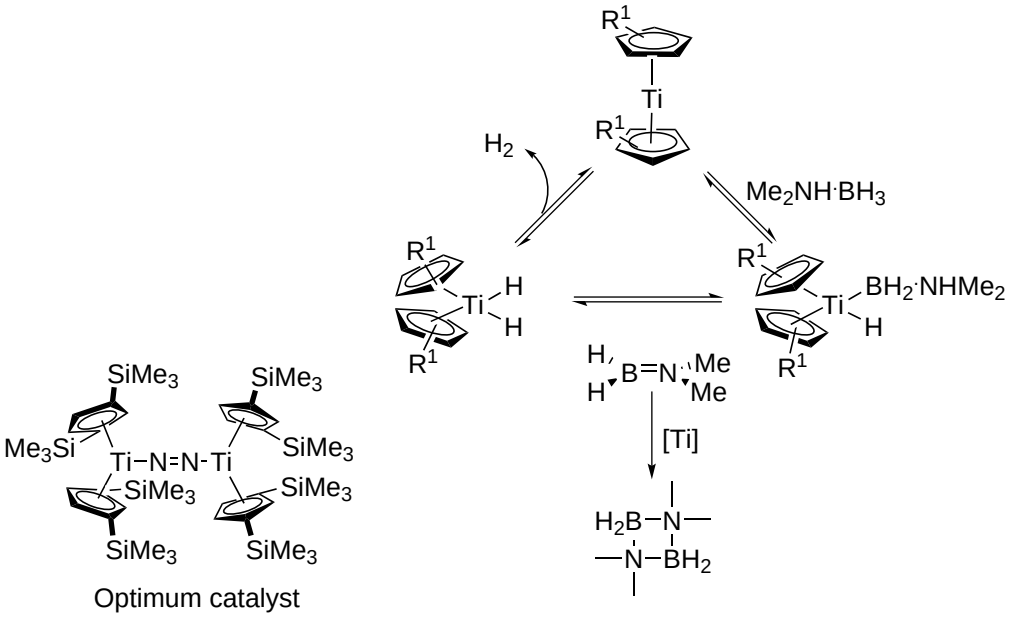


Figure 3.4: Pun's optimum group(IV) catalyst for DMAB dehydrogenation

Further studies were conducted again by Manners *et al.* for additional mechanistic insights. These revealed that as well as confirming that catalytic reactivity decreases down group(IV), even for analogous biscyclopentadienyl metal dichlorides, with the addition of butyl-lithium. The authors also reported further evidence to support the hypothesis that the mechanism was homogeneous. They showed that, as well as with proving the reaction continues despite the addition of mercury or after nano-filtration, the hypothesised titanium colloids were in fact not catalytically active for the reaction. From a combination of experimental and computational modelling the authors have proposed a two part catalytic cycle, initially similar to that proposed by Pun and co-workers, Fig. 3.4, but with an alternative secondary cycle, also catalysed by the titanocene(II) catalyst. In this cycle the initially linear amine-borane product Me_2NH-BH_2-NMe_2-BH_3 then undergoes a catalytic, ring closing, dehydrocoupling reaction to produce the cyclic products seen by ^{11}B NMR. Interestingly the authors also reported the use of the preformed Ti(II) catalyst $Cp_2Ti(PPH_3)_2$ which also catalyses the reaction to completion, although slightly longer reaction times are required to compensate for the required dissociation of the phosphines. Preformed Ti(III) catalysts showed no activity at all, even after 48 h.[133]

A different mode of activation was reported when certain group(IV) metals, such as cationic zirconium species, were used to form interesting frustrated Lewis pairs (FLPs) upon the addition of phosphinoaryloxides. The combination of the inherent reactivity of transition metal Lewis acids with the ability of FLPs to activate substrates *via*

ditopic activation showed some interesting potential in catalysis. Two zirconium FLPs were reported by the authors from the addition of 2-(diphenylphosphino)phenol to both biscyclopentadienyl zirconium dimethyl and bis(pentamethylcyclopentadienyl)zirconium dimethyl followed by protonation by [2,6-di-tert-butlypyridinium][$B(C_6F_5)_4$] to yield the sterically hindered transition metal containing linked frustrated Lewis pairs. Attempts to remove the remaining methyl group on the zirconium resulted in different products depending on the steric crowding on the cyclopentadiene ligand. For the unsubstituted Cp the production of methane showed coordination of the phosphine to the metal centre. When the pentamethyl-substituted Cp was used however, a chlorobenzene adduct was seen instead believed to be due to reaction with the solvent and no Zr-P bond was seen due to the steric interference. The comparative reactivity of the two catalysts was interesting as the non-substituted Cp catalyst was unable to heterolytically cleave H_2, at one atmosphere at room temperature, whereas the pentamethyl substituted catalyst could rapidly undertake this reaction to form the zirconium hydride phosphonium complex in high yields. Investigations with the two catalysts for the dehydrogenation of amine boranes was then attempted and it was reported that even at loadings of as low as 1 mol% the Cp catalytic system could smoothly convert dimethylamine borane into its dehydrogenated tetracyclic form within 10 min. The same reaction was investigated for the Cp* catalyst and although the reaction also ran to completion it was noticeably more sluggish requiring 8.5 h and 5 mol% catalyst loadings. Alternative amine boranes such as isopropylamine borane were also demonstrated to dehydrogenate readily, the use of ammonia borane however only gave traces of the borazine product although addition of an excess of cyclohexane produced the trapped hydroboration product Cy_2BNH_2. This showed a greater reactivity than previously reported for group(IV) catalysts. Mechanistic studies led the authors to suggest the catalytic cycle shown in Fig. 3.5, and it is important to point out that in contrast to the other group(IV) systems highlighted here the system is dependent on a high valency zirconium centre.[134]

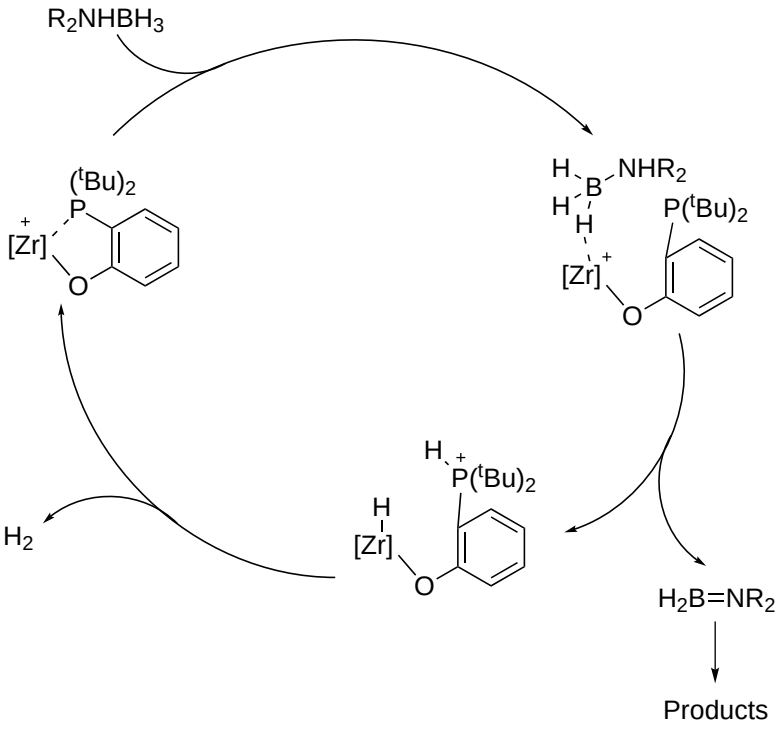


Figure 3.5: Zirconium FLP dehydrogenation of amine boranes

3.2.2 Palladium group metal catalysed amine borane dehydrogenation.

The first example in the scientific literature of metal catalysed dehydrocoupling of amine boranes was reported with the use of a series of rhodium precatalysts. The authors reported that the rhodium compounds form heterogeneous colloidal Rh(0) which is the active catalyst for the formation of cycloaminoboranes and borazines. Whilst several rhodium systems showed propensity for this sort of reactivity it was noted by the authors that when using $[\{Rh(cod)(\mu\text{-}Cl)\}_2]$, cyclooctane was seen to be present and is believed to be formed from the hydrogenation of the cod ligand. Noting this the authors set out to determine which rhodium precatalysts gave the optimal dehydrocoupling and hydrogenation ratios when an equivalent of cyclohexene was used in conjunction with DMAB and 2 mol% Rh catalyst loading. Both $[\{Rh(cod)(\mu\text{-}Cl)\}_2]$ and $RhCl_3$ showed complete dehydrocoupling and, provided the reactions were run in a closed environment, complete dehydrogenation whilst no conversions were seen in the absence of the catalyst. Interestingly when cyclooctadiene is used as the substrate in stoichiometric quantities there is no conversion seen for the $[\{Rh(cod)(\mu\text{-}Cl)\}_2]$ catalyst. It is believed the large excess of cod stops the dissociation of the ligand on the precatalyst, inhibiting the formation of the Rh colloids. In contrast when $RhCl_3$ is used there is no inhibition

to catalyst formation and so complete conversion is seen. It was noted that complete aggregation of the colloids over three days led to the production of bulk rhodium metal which when reintroduced to fresh conditions still showed catalytic activity in the reaction albeit at a slightly reduced efficacy, presumably due to the decreased surface area. The ability to run this reaction at room temperature with stoichiometric addition of amine boranes showed good potential as, although transfer hydrogenations are known for many metals with various substrates and hydrogen sources, few run at such low temperatures and most require an excess of one of the reagents.[135]

The authors decided to elucidate some mechanistic data for the reaction to determine if the reaction was heterogeneous as believed. The reason for this interest was that a clear red solution was produced when applying the methodology to the analogous dehydrocoupling of phosphine boranes. Comparatively, the dehydrocoupling of amine boranes resulted in a black opaque solution with a precipitate, suggesting the potential for two very different reaction mechanisms. The authors employed a variety of different techniques including; TEM, UV-Vis spectroscopy, reaction kinetics, mercury and fractional poisoning experiments and filtration experiments. Whilst some of the experiments cannot categorically determine if a reaction is one or the other, for example TEM might show the presence of metal particles even if they are not the active catalyst, the evidence when collated together showed very strong support for believing that the amine borane dehydrocoupling reactions were heterogeneously catalysed whilst the phosphine borane analogue underwent homogeneous dehydrocoupling catalysis. The difference in reaction methodologies is believed to be due to the ease of dissociation of the phophine-amine adducts in conjunction with phosphine ligation or possible poisoning of the catalyst. One of the most convincing pieces of data for the heterogeneous dehydrogenation of amine boranes was the analysis of the reaction kinetics which showed a sigmoidal kinetic curve characteristic of metal particle formation, both nucleation and autocatalytic particle growth. Additionally allowing the reaction to undergo this incubation period followed by rapid increase in catalytic activity once the conversion had reached approximately 50%; excess mercury was added and no further conversion of the substrate was seen beyond this time.[136]

Not all rhodium catalysts for the dehydrocoupling of the amine boranes proceed through pathways similar to those mentioned above. Weller and co-workers recently reported a monomeric Rh(I) species that upon the addition of amine boranes becomes reduced to a dimeric Rh(0) catalyst that displays previously unreported base stabilised boryl and hydride ligands with novel bridging modes seen for the amine borane, Fig. 3.6. This compound was demonstrated to catalyse the dehydrocoupling of DMAB quantitatively over 15 hours and mercury poisoning experiments showed no inhibition in reaction rate suggesting that the reaction is homogeneous in nature.

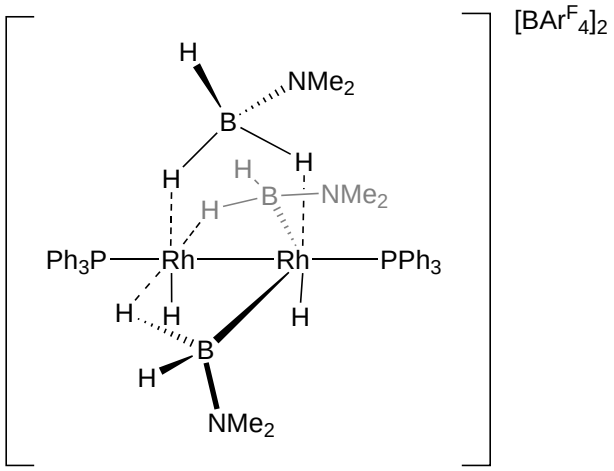


Figure 3.6: Rhodium dimer formed displaying unusual amine borane bonding motifs

Whilst many of these rhodium catalysed reactions were important preliminary studies into reaction mechanisms and dehydrocoupling products the catalytic turnover numbers and rate of hydrogen release were too low for amine boranes to be able to fulfil the necessary requirements as a hydrogen source for hydrogen fuel cells. Alternative metals were investigated as catalysts with iridium attracting a lot of attention as homogeneous catalysts based on iridium had been reported for the efficient dehydrogenation of alkanes; this is relevant as alkanes are isoelectric to amine boranes. One of the earliest reports of iridium based catalysts performing this reaction was the use of an iridium pincer complex, Fig. 3.7. This is able to catalyse the rapid dehydrocoupling of even ammonia borane to the cyclic pentameric form in low catalyst loadings (0.5 mol%) which had proved remarkably resistant to loss of hydrogen in many of the rhodium catalysed publications. In order to ensure the homogeneous nature of the catalyst, elemental mercury was added and the rate of reaction was not affected suggesting that the catalyst remains homogeneous throughout.[137]

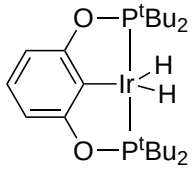


Figure 3.7: Highly effective iridium pincer complex

A more recent paper by Stevens *et al.* reported the use of an Ir(III) compound, [Ir(PCy$_3$)$_2$(H)$_2$][BAr$^F{}_4$], alongside computational studies to probe further the reactivity of the iridium catalysed reactions. Their work primarily focused on the substrate

dimethylamine borane as the products of dehydrocoupling are more readily identifiable by analysis due to increased solubility. The complex in question was not overly effective for the dehydrogenation of DMAB at room temperature ($t_{1/2}$ = 24 h) with reaction kinetics for this conversion showing neither a purely first or second order process in a closed system, the authors attributed this to the hydrogen produced provoking more complex kinetics. The iridium catalyst was also illustrated in this paper as catalysing the formation of the oligomeric form of the amine borane product. This couples the one molecule of DMAB with a molecule of the dehydrogenated dimethylamino-borane adduct which can then, with the loss of a second molecule of H_2 , cyclise to give the most stable dimeric form of the fully dehydrocoupled DMAB.[138]

3.2.3 Non-noble metal catalysts for dehydrocoupling of amine boranes.

There is a general shift throughout metal catalysis to move towards more sustainable catalytic systems both for environmental reasons but also due to the rapidly rising cost of the more scarce elements. An early example of a non-precious metal in the catalysis of amine borane dehydrocoupling was reported by Baker and colleagues where the combined use of Ni(0) complex of $Ni(cod)_2$ along with a range of NHCs. The NHCs were chosen as ligands due to the inherent strong donating quality they possess which is known to promote B-H activation. Of the NHCs investigated it was found that the Enders NHC (1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazole-5-ylidene) proved to be the most effective when used in conjunction with the nickel. The NHC showed no catalytic activity on its own whilst the rate of catalysis with the $Ni(cod)_2$ but without the NHC was considerably poorer. Mechanistic aspects of this reaction were probed and it was seen that for substituted amine boranes such as DMAB and $^tBuH_2NBH_3$ the reaction proceeded through the production of the monomeric amino-borane species. Kinetic isotope experiments showed that substitution of the hydrogens for deuterium, on either the boron or the nitrogen atom of the amine borane, decreased the rate of reaction. Full substitution produced the slowest rate of reaction, suggesting that both the B-H and the N-H bonds are broken in the rate determining step(s) as described in Fig. 3.8, where k_1 and k_2 are effectively equal.[139]

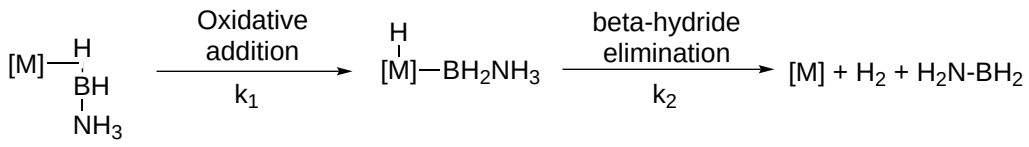


Figure 3.8: Ni-NHC catalyst proposed mechanism

Highly efficient though the nickel(0) -Enders NHC complex was, it was noted to be incredibly air sensitive and could never be isolated cleanly above 90 % encouraging the authors to form it *in situ*. Investigations were made to find a more robust nickel catalyst with alternative ligand systems. One of the more interesting reports from Trincado and co-workers considered the use of an amino-olefin ligand co-ordinated to both Ni(0) and Ni(I) complexes. These, in particular the Ni(I) catalyst, proved to be incredibly active for the dehydrogenation of DMAB where only 0.3 mol% of the catalyst was required to quantitatively release 1 equivalent of H_2 in under a minute in a 1M THF solution. The synthesis of these catalysts from the nickel trifluoroacetate precursor is represented in Fig. 3.9, with the structures having been determined by X-ray crystallography showing the pentacoordinated nickel(I) centre with the suggestion by the authors that the alkenes act to provide figuratively vacant coordination sites for catalysis.

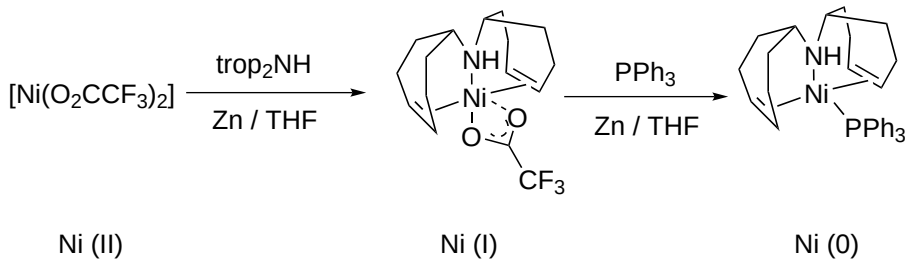


Figure 3.9: Synthesis of Ni(I) and Ni(0) olefin complexes

Further interest in non-precious metal catalysed dehydrocoupling was followed up in an interesting series of publications that looked at a very different mode of activation of the catalysts. The dehydrocoupling of a wide range of amine boranes was catalysed by group(VI) carbonyl compounds under the activation of photo-irradiation with $[Cr(CO)_6]$ proving to be a far more efficient catalyst than its tungsten analogue. Photo-irradiation was only required to activate the catalyst with hydrogen evolution occurring after the light source had been removed. The mechanism was believed to involve loss of one of the carbonyls to produce the active $[M(CO)_5]$ species, this then binds small amine boranes such as DMAB across the molecule and eliminating the hydrogen to form an amino-borane adduct. This can then undergo separate dimerisation whereas when large amine boranes are used then monomers are primarily formed. The full mechanism is described in Fig. 3.10, and this is based on a mixture of experiments and density functional theory (DFT) calculations.[140] The same group followed up on this work with investigations into the applicability of half sandwich metal carbonyl complexes to catalyse the reaction upon photo-illumination. Complexes were formed around; manganese, chromium and vanadium metal centres however the rate of hydrogen production was not as rapid as the exclusively carbonyl substituted catalysts. It was again noted that the chromium

complex was more effective than the analogous manganese catalyst.[141]

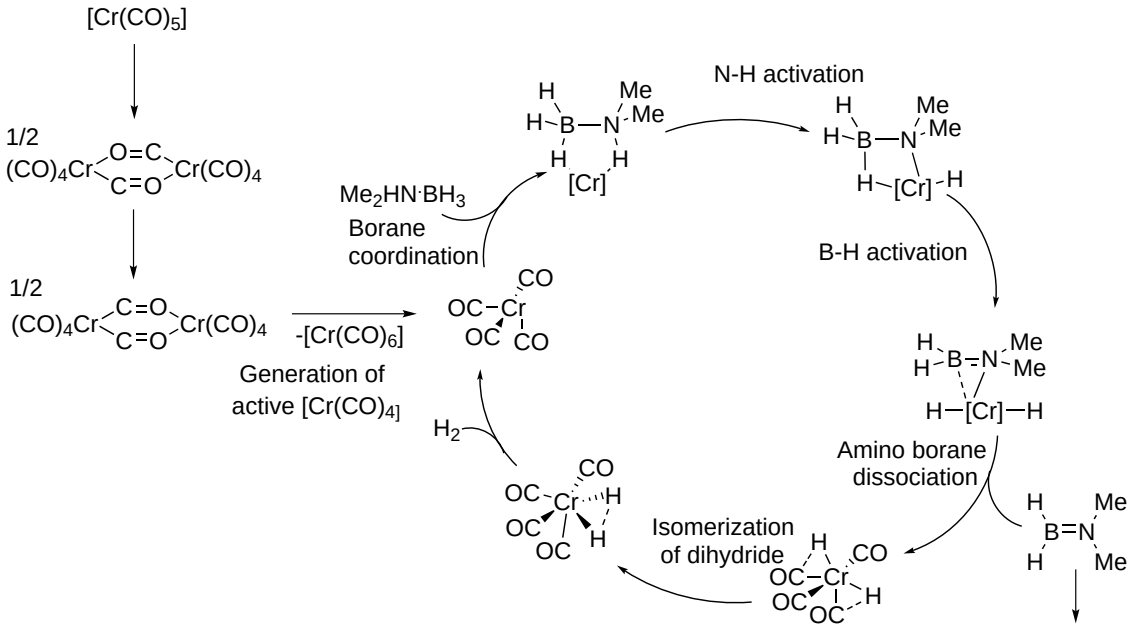


Figure 3.10: Proposed $Cr(CO_6)$ catalytic cycle

The final photo-induced catalytic system discussed was reported by Manners *et al.* whereby the dehydrogenation of a range of amine boranes was accomplished by the readily available, cheap and non-toxic precursor $[(CpFe(CO)_2)_2]$. This, in its unactivated form showed no catalytic activity, upon illumination however it produced quantitative dehydrogenation of DMAB at 5 mol% catalyst loading in 4 h at room temperature. It was noted by the authors that when sealing the system the reaction still proceeded to completion but the rate was significantly hindered; this was believed to be due to competition for the vacant site on the iron by the displaced carbon monoxide and the produced hydrogen. Alternative amine boranes such as diisopropylamine borane also reacted under these catalytic conditions although the conversion rates were much slower (*ca.* 100%, 15 h). Interestingly the authors reported that the dehydrocoupling of the primary methylamine borane initially after 3 h, led to the poly amino-borane $[MeNH\text{-}BH_2]_n$ with very high molecular weights of approximately 120,000, however upon prolonged exposure the major product that was isolated was *N*-methyl borazine, formed after the loss of further H_2. Whilst this catalytic system was not quite as effective as the metal carbonyl catalysts, reported by Manners above, the authors did investigate the reactivity against ammonia borane as well as the primary and secondary amine boranes mentioned. This substrate showed fairly rapid conversion (60%, 1 h) predominantly to the cyclolinear borane trimer whilst continued exposure suggested further dehydrogen-

ation to borazine.[142]

There have also been reports of heterogeneous methods of dehydrocoupling using sustainable transition metals. The group of Jagirdar in particular have focussed on the use of copper nano-particles and copper oxides for the release of dihydrogen from ammonia borane. The mechanisms investigated included both hydrolysis and methanolysis of ammonia borane and it was reported by the authors that the nano-particles they had produced by the solvated metal atom dispersion method showed greater activity than commercial Cu(0); this was reported to show negligible activity, whilst the oxidised nano-particles were the most active. Of the two routes for the production of hydrogen neither hydrolysis or methanolysis was noticeably better than the other although it was reported that the use of methanol inhibited the production of small amounts of ammonia that were seen in the case of hydrolysis.[143] A follow up paper by the authors looked at extending the range of metal sources that could be used to catalyse the dehydrogenation of ammonia borane. To this end they mechanically stirred ammonium borane with the bis-chloride salts of copper, nickel and cobalt at 60 °C all of which registered release of hydrogen well below the temperature of about 110 °C which is usually required for the loss of the first molecule of hydrogen. Of the three investigated only the copper(II) chloride showed instantaneous release of hydrogen with the other two salts requiring an induction period of approximately 3 h. Importantly it was noted that when the temperature was dropped to room temperature the copper system still released hydrogen although reaction times of 24 h were required to produce 1.4 moles of hydrogen with 20 mol% $CuCl_2$ and higher catalyst loadings did not extend this reaction further. The authors believe the rapid propagation step in this reaction is the formation of ammonium borochloride, as shown in the Equation: $H_3NBH_3 + CuCl_2 \rightarrow [NH_4]^+[BCl_4]^- + H_2 + 2Cu(0)$. This species can then go on to react with ammonia borane instigating its copper catalysed dehydrogenation at the lower temperatures.[144] One last paper by the group combines the two disparate uses of copper precursors by utilising the reductive powers of amine boranes, specifically ammonia borane, to reduce copper(II) chloride to the nano-particle where the polymeric product of the amine borane dehydrogenation has been shown to stabilise the particles formed by preventing agglomeration. This process was shown to transpose to other reductively formed nano-particles such as gold and silver.[145]

Over the last few months a report of similar solid supported gold nano particles has been published by Kaneda that has been shown to hydrogenate a wide range of organic functional groups, such as *N*-oxides, alkynes and unsaturated aldehydes chemoselectively under atmospheric or relatively low pressures of H_2 as well as groups such as nitro-arenes although these required much harsher conditions. The authors also describe the use of alternative hydrogen sources such as silanes, CO/H_2O combination and isopropyl al-

cohol with the nano-particles enabling greater chemoselectivity. The exact nature of the selectivity is not clear with the authors postulating that it may be due to a combination of factors such as the golds morphology, intrinsic selectivity of gold for specific functional groups and the role of the interactions between the gold and the support.[146]

3.3 Amine Boranes in Organic Synthesis.

A lot of the examples in the literature investigating the use of amine boranes in organic synthesis are based, as might be expected, on similar catalysts to those known to dehydrocouple amine boranes and so it follows that a lot of the pioneering work was accomplished with noble metal catalysts. An early example of this published by Heinz Berke and co-workers focusses on the transfer hydrogenation of olefins with a variety of rhenium compounds with different phosphine and simple alkanes ligated. Whilst all the Re catalysts investigated were shown to dehydrocouple ammonia borane to give borazine in good yields, the one shown in Fig. 3.11, gave the highest conversions and was demonstrated to catalyse the hydrogen transfer reaction shown. The reaction was fully homogeneous and the addition of a vast excess of bromine anions to the solution did not hinder the reaction. This suggests that the mechanism proceeds through transient loss of a phosphine ligand, as an excess of phosphine shut down the reaction, whereas in the absence of initially bound phosphine the reaction did not proceed at all.[147]

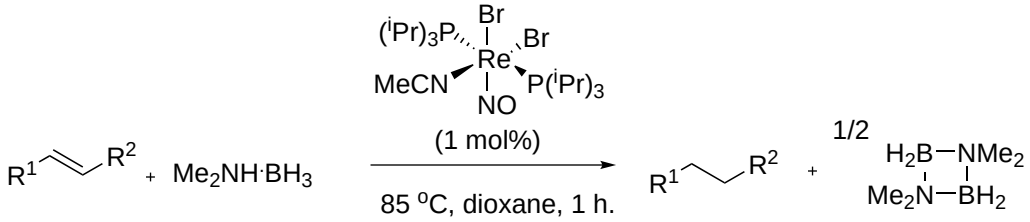


Figure 3.11: Re catalysed transfer hydrogenation of olefins

Other reports from the group regarding rhenium catalysed transfer hydrogenation from amine boranes followed including a detailed investigation on the mechanism which showed two similar competing catalytic pathways. The first involves the DMAB, which was chosen as the optimal substrate for mechanistic studies, binding to the vacant site of the Re(II) leading to a σ-complex, this then adds oxidatively forming the Re(III) species with concurrent phosphine dissociation. Reductive elimination occurs to generate the Re-B bond followed by β-hydride shift to regenerate the active catalyst. Reintroduction of the phosphine after the reductive elimination causes the transfer of the hydrogen to the substrate in this step.[148] In an attempt to improve the atom efficiency of the

reaction the authors investigated the use of alcoholysis to increase the quantities of hydrogen released from each molecule of amine borane. It was proven by the group that a single equivalent of amine borane in conjunction with three equivalents of ethanol could quantitatively reduce three equivalents of a terminal alkene. The reaction scope was expanded with a large range of amine boranes proving competent for this reaction with ammonia borane showing the highest k_{obs} with a similar catalyst to that used in the earlier papers. Increasing the reaction temperature to 70 °C, changing the alcoholic additive to IPA along with the addition of KO*t*-Bu as a co-catalyst could improve the system's reactivity and produce TOF's of ~400 h^{-1}.[149]

The use of rhodium colloids has also been reported for the transfer hydrogenation of alkenes and nitro-aryls compounds by Manners *et al.* The heterogeneous Rh/Al_2O_3 catalyst used by the authors is easily recoverable by filtration and was reported to show good chemoselectivity tolerating aryl iodides and bromides as well as epoxides under the reaction conditions in contrast to alternative reductive methodologies. A small substrate range was investigated with moderate to good isolated yields reported for the reduction of terminal, aliphatic and benzylic alkenes as well as aromatic nitro compounds, even when the reactions were carried out in an open environment, with the reactions requiring 48 h to achieve quantitative conversions. Internal alkenes and alkynes were investigated by the authors but the hydrogenations were not overly successful with only partial conversions into the desired products reported.[150]

An alternative report of a heterogeneous catalyst being used for the reduction of organic compounds was released by Stratakis and co-workers whereby titania-supported gold nanoparticles were used in the reduction of primarily aromatic nitro compounds to anilines. Titanium dioxide was found to be the best support for the nano-particles and allowed for catalyst loadings of 0.1 mol% when the reaction was run in ethanol. Good to excellent isolated yields were reported in short reaction times with a large range of functional groups being tolerated including; alkenes, esters, aromatic halides, and free acids although highly reactive groups such as aldehydes and ketones were also cleanly reduced requiring an excess of the ammonia borane. The methodology was also extended to the reduction of aliphatic nitro compounds at room temperature although the products formed were the alkylhydroxylamines rather than full reduction to the alkylamines. Reaction times were slightly longer than for the comparative aromatic nitro-group reductions and the yields whilst still high were lower. This was thought to be associated with the instability of the alkylhydroxylamines. To explore the reaction mechanism the authors synthesised some of the postulated intermediates and subjected these to the reaction conditions to observe if the reactions continued to completion. Ni-

trosobenzene was used in the reaction and was seen to form phenylhydroxylamine which rapidly reacts with another molecule of nitrosobenzene and the loss of water to form azaoxybenzene which is reduced to 1,2-diphenylhydrazine; this compound does not become reduced to give the expected aniline product under the reaction conditions suggesting the mechanism does not proceed through these routes. The authors suggest that the mechanism is instead proceeding through the formation of gold hydride species which reduce the aromatic nitro compound to an aromatic hydroxylamine rapidly and then the rate determining step is the further reduction of this hydroxylamine to the anilinic species. Evidence for this route is supported not only by the mechanistic information highlighted but also by the fact that gold nano-particles are not particularly effective at hydrogenations suggesting that molecular H_2 is not playing a role in the reductions.[151]

One very recent example of a highly efficient, although fairly complex, homogeneous catalyst was reported by Cazin *et al.* which makes use of a palladium metal centre ligated with phosphines and a NHC. Catalyst loadings of as low as 0.05 mol% were shown to enable the dehydrogenation of amine boranes and the tandem hydrogenation of unsaturated compounds. Primarily alkenes were investigated whilst internal alkynes showed selective reductions to cis-alkenes in high yields. Whilst esters and ethers were shown to be compatible in the reaction mixture carbonyls were more rapidly reduced to the corresponding saturated alcohol. 1,4-Cyclooctadiene was found to reduce to the fully saturated cyclooctane, when 1 mol% of the catalyst was used and the reaction run in methanol, whereas using a lower catalyst loading and changing the solvent to IPA resulted in the mono-reduced cyclooctene. The authors believe the catalyst reacts with the amine borane as shown in Fig. 3.12, to give the palladium hydride species shown which can then react with the substrate. The same catalyst has been shown to react in this way when exposed to molecular H_2 in a previous publication.[152]

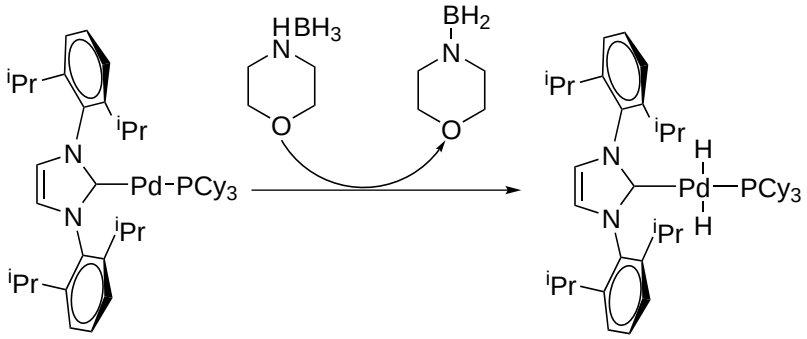


Figure 3.12: Activation of a palladium NHC catalyst with an amine borane.

3.4 Summary

The use of metals for the transient storage or movement of hydrogen has been a widely looked at area both within our own research group as well as further afield with wide ranging applications and sources of hydrogen having been investigated. Amine boranes in particular have attracted a lot of attention in recent years due to their high energy potential to mass ratio and they are being seen as a potential storage material for hydrogen which will be needed to meet the energy demands of the near future. The majority of the literature has focussed on the use of both metal and non-metal catalysts for the dehydrogenation of amine boranes with the release of molecular hydrogen for potential application in fuel cells and investigation into the structure and polymeric form of the amino-borane formed. Whilst early transition metals complexes around centres such as zirconium and titanium showed interesting potential as catalysts, in particular when in conjunction with FLPs, the majority of the literature surrounds the later transition metals and in particular the palladium group metals; ruthenium, rhodium, rhenium and iridium. Both homogeneous and heterogeneous catalysts have been explored in detail with more recent work having focussed on more sustainable first row metals such as nickel and chromium.

There have been very few reports of the use of catalysts for the activation of amine boranes in organic synthesis. The majority of examples described in the literature either require very expensive noble-metals or the use of complex synthesised catalysts. A significant proportion of reports have involved the use of the amine boranes for reductions of simple functional groups and investigating the relative chemoselectivities of different methodologies. There is still a dearth of research into the use of inexpensive, sustainable metal catalysts to expand the potential use of amine boranes as synthetic reagents beyond that which has already been reported.

3.5 Group interest into reductions

One recent area of interest for members of our group has centred around the production of unsymmetrical secondary amines from the reductive amination of nitriles. A colleague discovered that highly selective aminations could occur when a Pt/C (3 mol% by weight) catalyst was used in a continuous flow reactor with the addition of molecular hydrogen as the reductant. An alternative catalyst Pd/C was also investigated but showed lower selectivity for the desired nitrile amination although the conversion of the starting material was similar. It was reported that when a 1:1 ratio of nitrile to amine was used under the optimised reaction conditions, there was still a significant amount of the homo-coupled dibenzylamine produced from the reduction of the starting benzoni-

trile. Increasing the ratio of amine to 4:1 relative to the nitrile led to selective amination with only 4% of the homo-coupled product seen. A very wide range of primary aliphatic amines was reported to reductively aminate aliphatic and aromatic nitriles in excellent yields with high selectivities. Secondary and anilinic amines were also investigated with moderate to good isolated yields of the desired products being reported; heterocycles, aromatic halides and cyclic compounds were all shown as being tolerated. Of note was that there was no discernible loss of activity of the Pt/C catalyst over time and that the reaction only required low residence times of 10 s.[153]

Whilst there is growing interest in continuous flow reactions the majority of industrial applications still proceed through batch processes. Alternative work by another member of the group investigated the reduction of a greater scope of organic functional groups using, in this case, a ruthenium catalyst as these had shown themselves to be highly effective for many transfer hydrogenation reactions. Dimethylamine borane (DMAB) was chosen as the hydrogen source in this instance with a catalyst screen showing that both $[Ru(p\text{-cymene})Cl_2]_2$ and $Ru(PPh_3)_3(CO)H_2$ could quantitatively reduce acetophenone at 70 °C within 24 h. $[Ru(p\text{-cymene})Cl_2]_2$ was chosen to be taken forward for further optimisation due to its considerably lower cost. A selection of ketones and aldehydes was reduced in good yields with both aromatic and aliphatic carbonyls tolerated. The scope of the reaction was investigated with a range of imines showing reduction, with moderate isolated yields in 24 h again in THF at reflux. Aromatic oximes were also shown to undergo reduction although instead of reducing to the primary amine as might be expected or alternatively rearrangement to the primary amide, as had been seen from some of the previous hydrogen borrowing literature, they were reported to form secondary amines. It was postulated that the reaction involved initial reduction of the hydroxylamine to a primary amine, this is then able to react with another molecule of oxime to form an imine, with reversible loss of hydroxylamine. This imine is very susceptible to reduction to yield the secondary amine which was seen in moderate isolated yields. The authors also reported the reduction of some nitriles, a secondary alkene and some aromatic nitro compounds all in good isolated yields. One of the most interesting reports from the paper was that the introduction of enantiomerically pure ligands to the ruthenium centre could be used to reduce aromatic ketones stereoselectively with moderate enantiomeric excesses reported as shown in Fig. 3.13.[154]

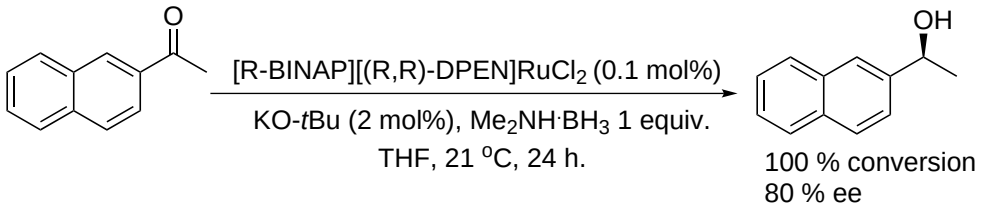


Figure 3.13: Enantiomerically pure reduction of ketones using DMAB

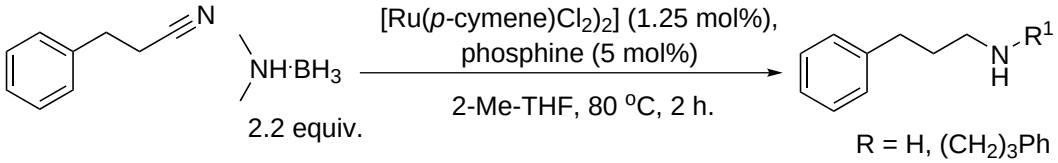
Finding a homogeneous methodology for the reductive amination of nitriles with amines or amine precursors would be desirable enabling the expansion of the applicability of the process for batch production. Building upon previous work within the group focussing on transfer hydrogenation or the use of amine boranes as a source of hydrogen would be optimal and so these routes were investigated initially. The results given in the next section summarise the optimisation of this process and a summary of a novel method for reductions. The use of aromatic nitro compounds as precursors for anilinic species was investigated due to their abundance and ease of formation.

3.6 Optimisation

3.6.1 Ruthenium catalysed reductions

The first stage of optimisation was to determine which hydrogen source was going to be most suitable for the reaction. This involved investigating the two most commonly used ruthenium catalysts, $[Ru(p\text{-cymene})Cl_2]_2$ and $Ru(PPh)_3(CO)H_2$ which had both shown propensity for amine borane dehydrogenation as well as transfer hydrogenation using a variety of potential hydrogen sources. It was found that amine boranes were by far the most reactive under the reaction conditions and so further investigations were made using the $[Ru(p\text{-cymene})Cl_2]_2$ catalyst with a selection of amine boranes.

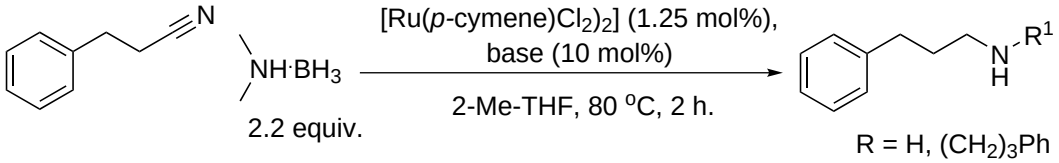
The choice was initially made to explore the reduction of nitriles as they are inherently stable and 3-phenylpropionitrile was selected as the substrate. As phosphines are well documented to alter the efficacy of ruthenium catalysts a screen of phosphines with wide ranging properties was conducted with the results set out in Table 3.1.



Entry	Phosphine	Conversion by ^{1}H NMR
1	Ethylenebis(diphenylphosphine)	13%
2	Propylenebis(diphenylphosphine)	21%
3	Butylenebis(diphenylphosphine)	20%
4	Pentylenebis(diphenylphosphine)	47%
5	Tri-*p*tolylphosphine	58%
6	Tri-2,4,6-trimethylphenylphosphine	18%
7	DPEPhos	17%
8	Xanthos	19%
9	1,4-Bis(dicyclohexylphosphino)butene	55%
10	Diphenylphosphinamide	34%
11	Trimethylphosphite	32%
12	Tri-4-(trifluoromethyl)phenylphosphine	19%

Table 3.1: Phosphine screen for the Ru catalysed reduction of 3-phenylpropionitrile

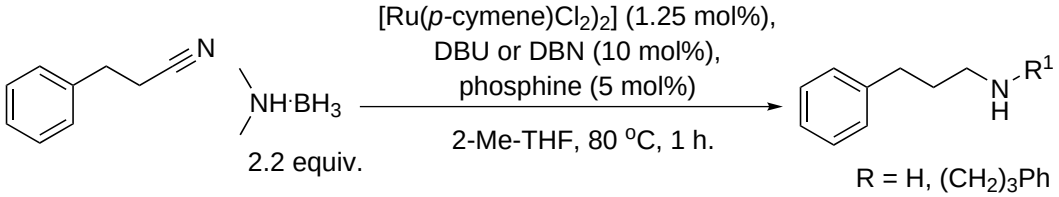
As can be seen there is a significant variation when different phosphines are used with tri-*p*-methyl phosphine proving to be the most effective of those investigated. Similarly the use of different bases can alter the reactivity of catalysts and so a screen of common organic and inorganic bases was investigated in the absence of any phosphine additives These results, shown in Table 3.2, demonstrate that whilst some of the inorganic bases, in particular sodium hydroxide and sodium carbonate showed high conversions, the most effective base investigated was 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), Entry 5.



Entry	Base	Conversion by ^{1}H NMR
1	K_2CO_3	43%
2	NaOH	67%
3	KOH	35%
4	Cs_2CO_3	30%
5	DBU	73%
6	KO^{t}Bu	45%
7	Et_3N	43%
8	Na_2CO_3	55%
9	LiOH	28%
10	No base	54%

Table 3.2: Base screen for the Ru catalysed reduction of 3-phenylpropionitrile

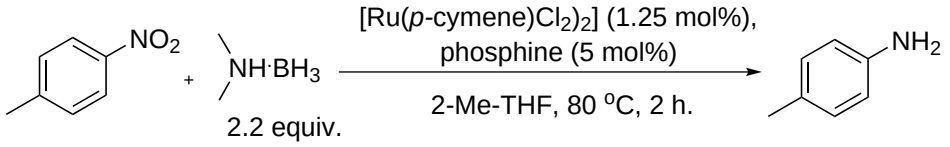
Comparative reactions were run with most effective base DBU and a similar analogue DBN run alongside the addition of a selection of the most effective phosphine catalysts to determine if any synergistic effects could be seen. The length of the reaction times was decreased to 1 h to ensure ease of comparison and the results, shown in Table 3.3, suggest that there is in fact no discernible synergistic benefit of using a combination of base and phosphine since the two bases produce the greatest conversions when used in isolation although there was no large significant difference between the two conversions.



	Conversion by ^{1}H NMR	
Phosphine	Base : DBU	Base : DBN
Tri-*p*-tolylphosphine	24%	24%
1,4-Bis(dicyclohexylphosphino)butene	35%	51%
Pentylenebis(diphenylphosphine)	14%	20%
No Phosphine	79%	74%

Table 3.3: Combination of base and phosphine additives

One of the important intentions of the project was to be able to extend the methodology to enable the reduction of aromatic nitro compounds to the respective anilinic compounds cleanly and efficiently with the intention for the aniline produced to be able to play a role in the amination of organic nitriles in a one-pot reaction. A new phosphine screen was conducted to ensure that the conversions seen for the reduction of 4-nitrotoluene, the chosen substrate, were not enhanced by the addition of a phosphine in contrast to the results seen for the reduction of a nitrile. The results in Table 3.4 clearly show the detrimental effect of the addition of a phosphine relative to the control without an additive (Entry, 12), possibly suggesting that the binding to the ruthenium of the phosphine is too great, inhibiting the catalyst.



Entry	Phosphine	Conversion by ^{1}H NMR
1	Ethylenebis(diphenylphosphine)	28%
2	Propylenebis(diphenylphosphine)	28%
3	Butylenebis(diphenylphosphine)	26%
4	Pentylenebis(diphenylphosphine)	44%
5	Tri-*p*tolylphosphine	60%
6	Tri-2,4,6-trimethylphenylphosphine	65%
7	DPEPhos	60%
8	Xanthos	56%
9	1,4-Bis(dicyclohexylphosphino)butene	62%
10	Diphenylphosphinamide	54%
11	Tri-4-(trifluoromethyl)phenylphosphine	49%
12	Control (no phosphine)	71%

Table 3.4: Phosphine screen for the Ru catalysed reduction of 4-nitrotoluene

The next step was to determine if the two reactions could be conducted together and to investigate the degree of coupling that occurs between the reduced nitro species and the starting nitrile. It is important for the nitro compound to reduce to the aniline as rapidly as possible to enable it to attack the nitrile forming an amidine intermediate. This intermediate could then ideally be reduced to give the desired amination product with the addition of two further equivalents of hydrogen as shown in Fig. 3.14.

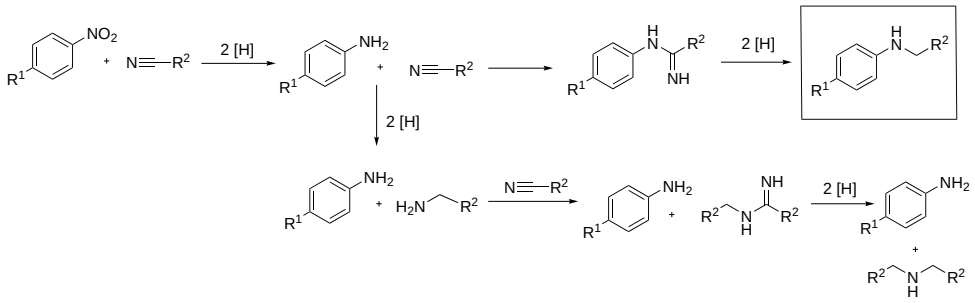
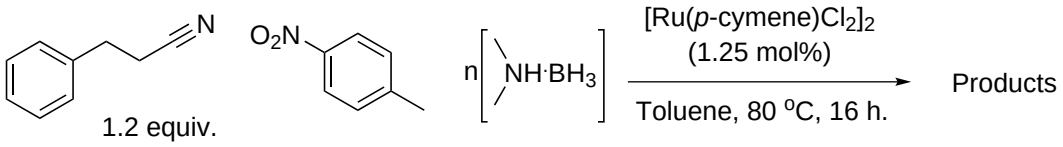


Figure 3.14: Possible mechanistic pathways in the reductive amination of a nitrile

Of note is the possibility of overly rapid reduction of the nitrile as this will produce a primary amine which is more nucleophilic than the aniline produced from the nitro reduction. This is more likely to attack any remaining nitrile and form the homo-coupled, symmetrical secondary amine. It was thought that the concentration of amine borane that was used might be one of the variables that would most affect the ratio, of desired product compared with homo-coupled product, so a series of reactions introducing both substrates into the reaction mixture along with varying equivalents of amine borane was conducted with the results shown in Table 3.5.



Entry	Equivalents of DMAB	% Reduction of Nitro	% Coupled product
1	4	41	17
2	5	53	13
3	10	55	7
4	15	98	0

nb. Conversions as seen by ^{1}H NMR.

Table 3.5: Variation in equivalents of amine borane for reductive amination

What is clear from the results, especially compared with those given in Table 3.6.1 is that the presence of the nitrile slows down the reduction of the 4-nitrotoluene to toluidine. This may be occurring in away analogous to the addition of phosphine whereby the ligands retarded the reaction, possibly by coordinating to the ruthenium and occupying potential vacant sites. It was postulated at this point that there might be a mechanism by which the reaction rate could be enhanced with the addition of a co-catalyst. The reasoning for this was two fold; firstly the co-catalyst might help coordinate some of

the nitrile groups, releasing coordination sites on the ruthenium centre and secondly the co-catalyst might be able to withdraw electron density from the nitrile, increasing its electrophilic nature and hopefully leading to greater attack by the poorly nucleophilic aniline, a potential mechanism for which is shown in Fig. 3.15.

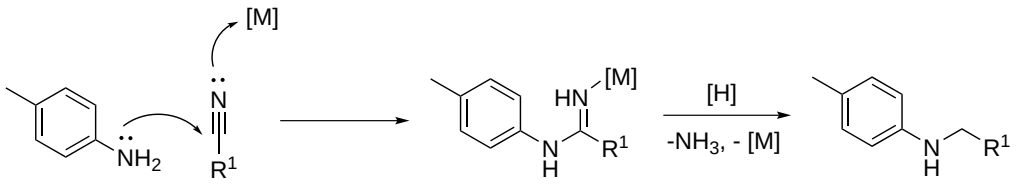
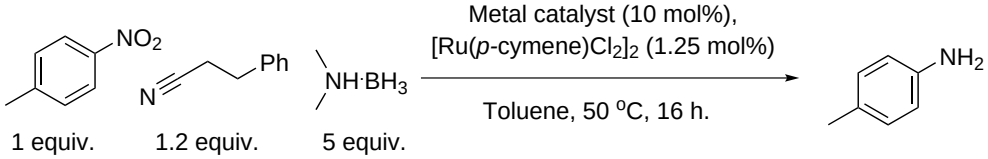


Figure 3.15: Postulated mechanism of Lewis acid co-catalysis

The results for the screen of metal co-catalysts are given in Table 3.6, with just the conversions of the nitro given although the nitrile was also present. The results were quite surprising in that they showed very little alteration to the ruthenium only catalysed rate even with co-catalysts such as zinc triflate which are well known for coordinating nitriles. The exception to this pattern was Entry 5 where the copper acetate catalyst showed complete reduction of the 4-nitrotoluene under the reaction conditions.



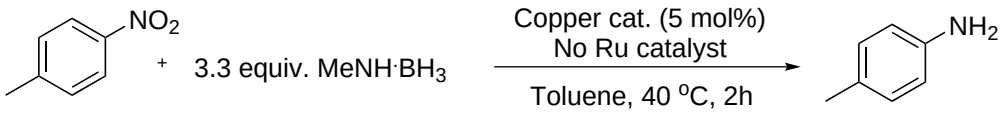
Entry	Co-catalyst	Conversion of Nitro by ^{1}H NMR
1	$Sc(OTf)_3$	72%
2	$Zn(OTf)_2$	79%
3	$ZnCl_2$	73%
4	$Ti(OiPr)_4$	79%
5	$Cu(OAc)_2$	100%
6	$FeCl_3$	68%
7	No co-catalyst	75%

Table 3.6: Ru with co-catalyst screen of nitro reduction

3.6.2 Copper catalysed reductions

A repeat of the earlier reaction was conducted at a lower temperature (40 °C) for less time (4 h) to determine a more accurate comparison of the copper co-catalyst's efficiency. Even under these milder conditions there was quantitative reduction of the nitro group

with the next best co-catalyst, scandium(III) triflate, recording only 33% conversion. The reduction of the nitrile had not progressed very far for any of the reactions under the mild conditions which, although discouraging, did show that the presence of a nitrile did not inhibit the catalyst function too much. Considering the huge improvement in the reaction rate compared with the ruthenium and ruthenium with addition of a co-catalyst reactions, it was thought that a separate copper mediate reaction might be progressing and so the next stage of optimisation was to determine if the nature of the copper salt in the absence of ruthenium had an effect on the reaction. The results for the copper salt screen are shown in Table 3.7, and what is clear is that almost all of the salts and oxides investigated worked with a good degree of success with the exception of copper(I) iodide.



Entry	Catalyst	Conversion by ^{1}H NMR
1	$Cu(OAc)_2$	66%
2	$CuCl_2$	66%
3	$Cu(NO_3)$	44%
4	Cu_2O	73%
5	CuO	84%
6	$Cu(OTf)_2$	52%
7	CuBr	73%
8	CuI	0%
9	CuCl	50%
10	Cu-TMEDA[a]	100%
11	No catalyst	0%

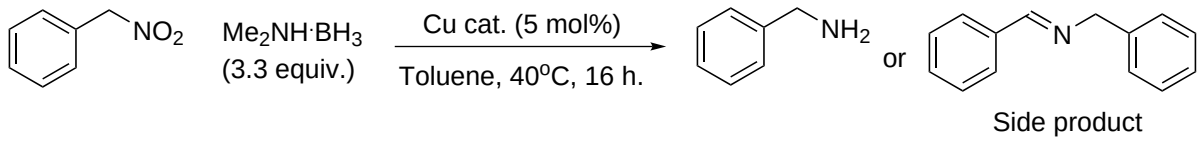
a) 10% Copper as a dimer

Table 3.7: Copper salt screen for the reduction of 4-nitrotoluene

3.6.3 Reduction of aliphatic nitros

Whilst the production of anilines from aromatic nitro compounds was seen to proceed cleanly and to completion under certain reaction conditions, it was thought to be of interest to determine whether the methodology could be extended to the reduction of aliphatic nitro compounds. The reduction of nitro groups becomes a lot more challenging to complete cleanly when there are hydrogens in the α-position as this allows for tautomerisation of the reduction intermediates which can produce undesired side products. Nitromethyl benzene was chosen as the representative substrate and dimethylamine

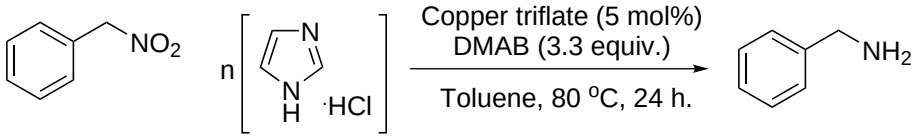
borane as the hydrogen source as it had proved the most adept for the aromatic nitro reductions. A quick copper salt screen from the catalysts that had shown good potential previously showed very low conversions to the desired benzylamine, as seen in Table 3.8, with large amounts of side product formed and in particular the homo-coupled imine formation.



Entry	Copper catalyst	Conversion to benzylamine (%)	Conversion to imine (%)
1	Cu-TMEDA	3	45
2	CuBr	2	15
3	CuO	3	36
4	$Cu(OTf)_2$	2	2
5	$Cu(OAc)_2$	3	9
6	No catalyst	0	0

Table 3.8: Catalyst screen for the reduction of nitromethyl benzene

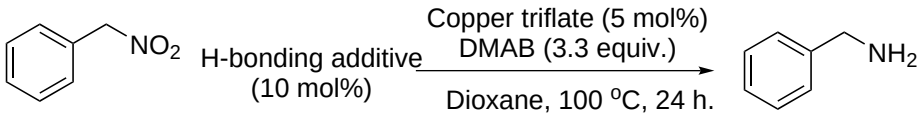
Whilst none of these reactions gave good conversions to the product it was decided to persevere using copper triflate as the catalyst since, although this demonstrated poor reduction, the ratio of product to side-product was the highest. The acidity of the solution is known to affect the tautomerisation of nitro compounds and so the addition of varying concentrations of imidazole hydrochloride was investigated and the results displayed in Table 3.9. Unfortunately it is clear that addition of the salt only serves to inhibit the reaction however for these investigations the reaction temperature was raised and the reaction time extended to 24 h, this increase having an interesting effect of increasing the catalyst only conversion from 2% up to 20% as seen in Entry 6.



Entry	Equivalents of Imidazole.HCl	Conversion to benzylamine
1	2	0
2	1.5	0
3	1	4
4	0.5	13
5	0.1	15
6	0	20

Table 3.9: Imidazole concentration effect on the reduction of nitromethyl benzene

A solvent screen was conducted which showed that more polar solvents were favourable to the reaction conditions; this led to the possibility of using hydrogen bonding co-catalysts to enhance the selectivity of the reactions. A selection of different known hydrogen bonding molecules was investigated as shown in Table 3.10, and it was apparent that the selectivity of the reaction was increased by addition of an additive coupled with a further increase in the reaction temperature. Of the additives investigated the urea and thiourea derivatives proved the most successful with *N,N*-diphenyl urea showing the greatest conversion to the desired product, Entry 6.



Entry	H-bonding additive	Conversion to benzylamine
1	Binol	18%
2	Adenine	19%
3	Guanidine	32%
4	*N,N*-diphenyl thiourea	27%
5	*N,N*-diisopropyl thiourea	43%
6	*N,N*-diphenyl urea	47%

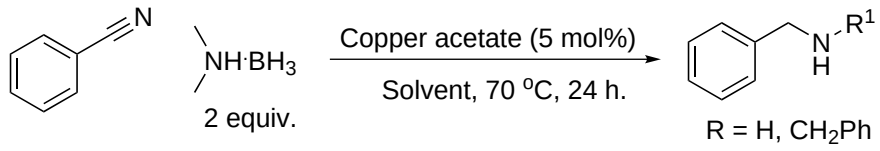
Table 3.10: Hydrogen bonding additives in the reduction of nitromethyl benzene

Variations in the solvent for the hydrogen bonding catalyst reactions and the addition of other additives such as phosphines, which had shown some enhancement to conversions for alternative copper catalysed amine borane reductions, did not produce any great improvement in conversions from those shown in Table 3.10. Reducing the

concentration of the copper catalyst was hoped to increase selectivity but only had the effect of reducing conversion. The optimisation for the reduction of aliphatic nitro compounds was halted at this point with focus prioritising on the reduction of alternative functional groups.

3.6.4 Optimisation of the aqueous reduction of nitriles and imines

As the methodology for the reduction of aromatic nitro groups proved both flexible as well as very efficient it was decided to focus on the reduction of nitriles and imines. Imines are important as their production is a postulated intermediate in the amination of nitriles and finding a methodology that produces the secondary amine in a clean and efficient manner from these would be key to optimising the whole process. As polar solvents had proved important for the reduction of aliphatic nitro groups a solvent screen was conducted for the reduction of benzonitrile. It was found that water was the optimum solvent, as seen in Table 3.11, this could be at least in part due to the added potential of the water to hydrolyse the amino-borane product releasing further quantities of hydrogen. Of note is the comparatively low conversions seen for the reactions run in ethanol, Entry 5, which would have been thought to aid the solubility of the reagents relative to water as well as being more nucleophilic suggesting it would be more efficient at the alcoholysis of the amino-borane.

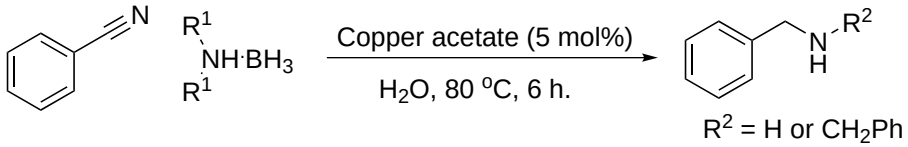


Entry	Solvent	Conversion by ^{1}H NMR
1	Toluene	20%
2	THF	57%
3	Hexane	50%
4	Water	93%
5	Ethanol	27%
6	DCE	25%

Table 3.11: Solvent screen for the copper catalysed reduction of benzonitrile

The next key step for optimisation was to determine which of the amine borane reductants was best under the reaction conditions and whether a sub-stoichiometric quantity would suffice. The three investigated were all commercially available reagents and from the results in Table 3.12 it is apparent that dimethylamine borane and ammonia

borane were both very efficient with dimethylamine borane showing the highest conversions although the selectivity for primary amine production was slightly lower. The results in Table 3.12 also suggest that under these conditions a stoichiometric amount of the reductant is required at least for challenging substrates such as nitriles.

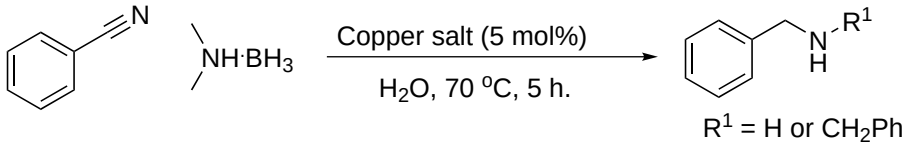


Entry	Amine borane	Equiv. of amine borane	Conv. from SM	Conv. to 1° amine [a]
1	NH_3 BH_3	2.2	82%	50%
2	Me_2NH BH_3	2.2	96%	43%
3	$^tBuNH_2$ BH_3	2.2	0%	0%
4	Me_2NH BH_3	0.66	22%	13%

a) Conversion based on NH_2 peak in the ^1H NMR.

Table 3.12: Amine borane screen for the reduction of benzonitrile

With the optimisation of the solvent and amine borane complete, a repeat of the investigation of copper salts was conducted to ensure that the correct one for these conditions was chosen. The results given in Table 3.13, show that copper triflate was the optimum catalyst for use in water reactions, Entry 2, as it could reduce the benzonitrile quantitatively and was the cleanest reaction seen to convert the starting material into mono-,di- or tri-benzylamine with copper sulfate also producing high conversions with a slightly greater level of selectivity, Entry 5. The reaction conditions have been moderated from previously with both reaction temperature and reaction length decreased.



Entry	Copper Salt	Conversion to amine	Conversion to 1° amine
1	$Cu(OAc)_2$	39%	21%
2	$Cu(OTf)_2$	94%	33%
3	CuBr	16%	11%
4	CuO	79%	35%
5	$CuSO_4$	82%	45%
6	CuCl	63%	39%
7	$(MeCN)_4CuOTf$	59%	12%
8	No Copper	0%	0%

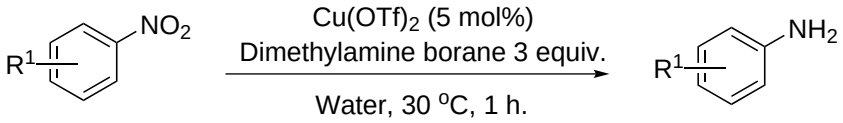
Table 3.13: Copper salt screen for the aqueous reduction of benzonitrile

The optimised conditions from above were investigated for the reduction of aliphatic nitriles that do not have the electron withdrawing effect of the aromatic ring enhancing their reactivity. Both copper triflate and copper sulfate were used as catalysts for the reduction of benzylcyanide and again copper triflate gave the greatest reductions, 64% conversion when run in water and 58% when in a 1:1 water to ethanol mix, whereas copper sulfate yielded conversions of 50% and 61% respectively. Important to note was that there were only secondary and tertiary benzylamines found when the samples were analysed by mass spectrometry suggesting facile nucleophilic attack at the nitrile by the amines produced from reduction. Imine reduction was also investigated using the two catalysts under the same reaction conditions with quantitative conversion to the expected amine seen for both catalyst systems within 45 min whilst the uncatalysed reaction had only reached 9% in this time.

The results of the optimisation showed that copper catalysts could be used to catalyse the dehydrogenation and hydrogen transfer reduction of both unsaturated nitrogen containing functional groups as well as aromatic nitro compounds; aliphatic nitro compounds also showed reduction albeit with less success at selectivity. These results were taken on to isolate a range of compounds formed from the reduction of nitriles and imines with attempts made to isolate the reductive amination product of a simple amine with a range of nitriles. The ability to employ the methodology for the reduction of alternative organic functional groups is also discussed.

3.7 Results

The first functional group investigated for reductions were aromatic nitro groups which had been seen to reduce well in the optimisation steps. From the results given in Table 3.14 it is apparent that some steric bulk around the nitro group could be tolerated as could aromatic nitros without the inductive effect of the methyl group. Tolerance of a free aniline group was also compatible as might be expected considering the product of the reaction; the isolated yield of the product however was considerably diminished and this is thought to be due to degradation. Some substrates that did not give good conversions were ones with strongly electron withdrawing groups in the *para*-position such as 4-nitrobenzamide and 4-nitrosulfonamide. Aromatic halogens were also tolerated without showing signs of reduction under the reaction conditions.



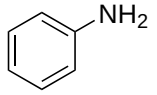
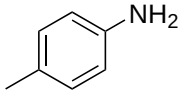
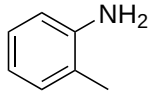
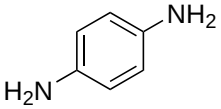
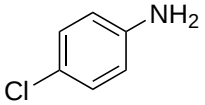
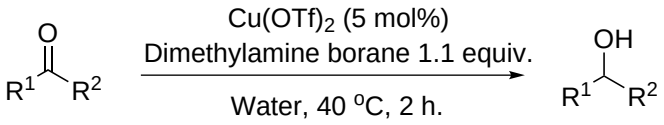
Entry	Aniline formed	Product ID	Isolated Yield (%)
1		**3.1**	86
2		**3.2**	100
3		**3.3**	86
4		**3.4**	34
5		**3.5**	94

Table 3.14: Aromatic nitro reduction screen

The next functional groups to be investigated were carbonyls as these should also be fairly facile to reduce. Primarily aromatic carbonyls were investigated although the aliphatic 2-heptanone also showed good potential for reduction. As the results on Table 3.15 show both electron poor and electron rich aromatic ketones can be reduced as well

as the aromatic aldehyde, benzaldehyde. Whilst the presence of aromatic halogens were tolerated the presence of an aromatic nitro group produced a considerable amount of side products with both the solely nitro-reduced product as well as the product formed when both functional groups reduce being seen resulting in low yields of the desired alcohol, entry 4.



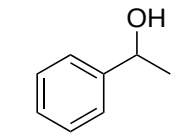
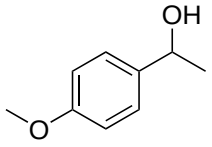
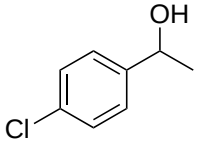
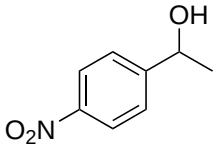
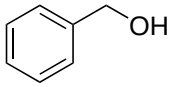
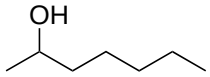
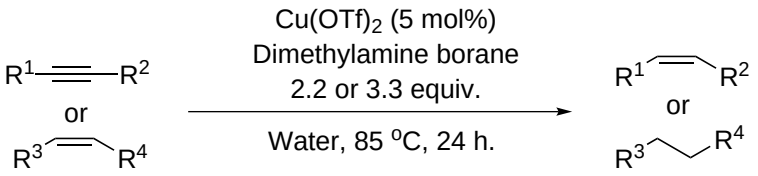
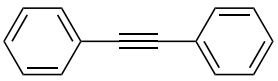
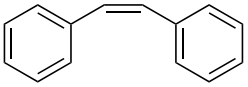
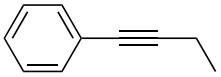
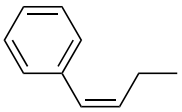
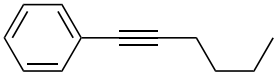
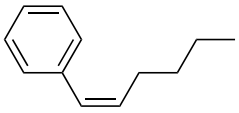
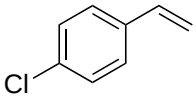
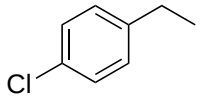
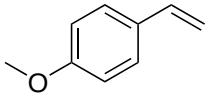
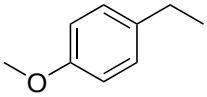
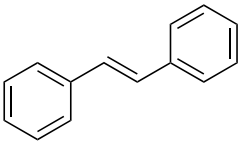
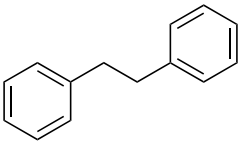
Entry	Alcohol formed	Product ID	Isolated Yield (%)
1		**3.6**	99
2		**3.7**	79
3		**3.8**	100
4		**3.9**	39
5		**3.10**	75
6		**3.11**	84

Table 3.15: Carbonyl reduction screen

More challenging substrates were then looked at to determine the scope of the reaction with unsaturated hydrocarbons the next to be investigated. Interestingly it was seen that alkynes were considerably easier to reduce than alkenes which enables selective reduction of the alkynes to the corresponding *cis*-alkene as determined by ^{1}H NMR. The reaction was tolerant for aromatic alkynes such as the sterically crowded

bis-phenylacetylene, from which *cis*-stilbene could be isolated in quantitative yields, as well as internal alkynes with various aliphatic groups attached. In contrast when purely aliphatic alkynes were used, a mixture of products were seen with both 1-octyne and 2-octyne producing intractable mixtures. The reduction of alkenes was also briefly investigated and again the aromatic styrene systems produced the best results with 4-chlorostyrene showing high conversions to the alkylated analogue. Sterically hindered alkenes such as both *cis*- and *trans*-stilbene showed themselves to be unreactive under the reaction conditions.



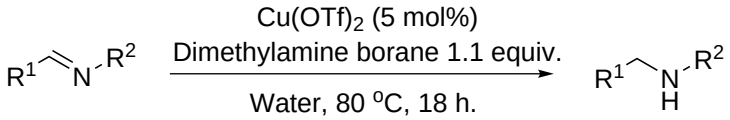
Entry	Substrate	Product	Product ID	Yield (%)
1			**3.12**	97
2			**3.13**	98
3			**3.14**	88
4			**3.15**	71[a]
5			**3.16**	72[a]
6			-	0

a) Conversion based on ^{1}H NMR.

Table 3.16: Reduction of unsaturated hydrocarbons

The final independent functional group investigated was the imine groups functionality with a variety of imines having either been purchased or made from the the condensation of the corresponding amine and carbonyl. In a similar fashion to the results seen

for the reduction of other functionalities the reaction conditions tolerated the presence of aromatic halogens but could not tolerate the additional presence of an aromatic nitro group producing a range of side products. Both *N*-benzylic and and *N*-anilinic imines showed reductions, Table 3.17, as did the *N*-isopropyl aliphatic analogue. The isolated yields are significantly lower than the conversions seen, this is due to the method of isolation whereby acidification with ethereal HCl produced the salt of the amine with some loss through filtration.



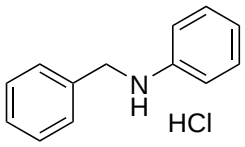
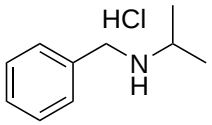
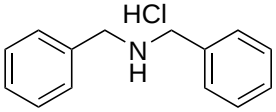
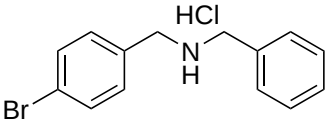
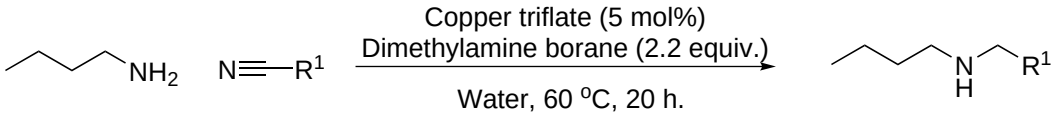
Entry	Product	Product ID	Isolated Yield (%)
1		**3.17**	83
2		**3.18**	70
3		**3.19**	65
4		**3.20**	87

Table 3.17: Reduction of imines

As the methodology had proved successful for the reduction of a range of functional groups it was decided to investigate whether the reaction could be expanded to selectively reduce the intermediate formed from the attack of a nitrile by an amine. Although the reductions of nitro compounds had been seen to rapidly reduce to the aniline in a far quicker rate relative to a nitrile reduction it was decided to investigate the reactions with the addition of an amine in rather than forming one *in situ*. This was to overcome both the inherent lack of nucleophilicity of anilines, formed from aromatic nitro reduction, as well as to avoid interactions with the side products that would be formed by the reduction of aliphatic nitro groups.

In order to determine which nitrile substrate was the most suitable, butylamine was

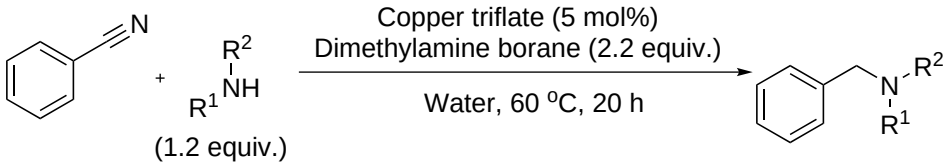
added to a solution of copper triflate and a range of nitriles in water followed by the reductive amine borane. The results for this screen are seen in Table 3.18 and it is apparent that the aromatic nitriles are far more favourable for amination. This could be either due to a greater intrinsic reactivity of the nitrile as an electrophile due to the electron withdrawing effects of the aromatic ring or due to the ability to resonance stabilise any intermediates formed from the attack of the amine, prolonging the lifetime of the reactive intermediate.



Entry	Nitrile	Conversion (%)
1	Benzonitrile	75
2	Benzylcyanide	26
3	Heptylcyanide	5
4	4-Methoxybenzonitrile	76
5	4-Tolunitrile	68

Table 3.18: Nitrile screen for reductive amination

A selection of simple, low boiling amines was then run alongside benzonitrile to determine the scope for addition. Whilst some of the ones chosen showed high conversions to the desired products there was unfortunately not the level of general applicability desired. Table 3.19 shows the conversions and yields achieved, as might be expected the primary butylamine as well as pyrrolidine, which is particularly nucleophilic due to ring strain, showed good selectivity for the amination.



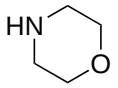
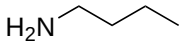
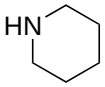
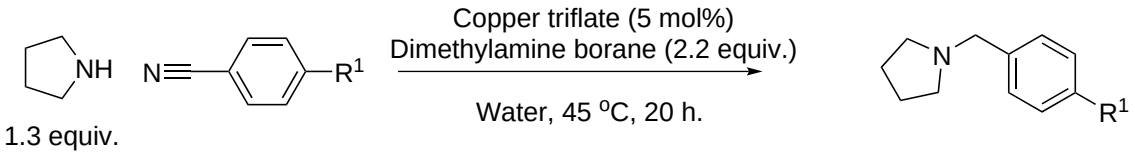
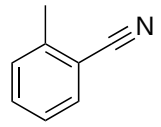
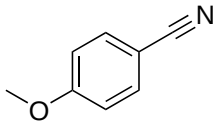
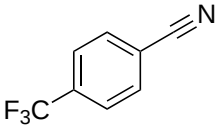
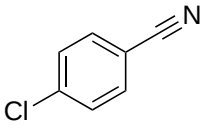
Entry	Amine	Product ID	Conversion (Isolated yield)
1		-	16%
2		**3.21**	78% (47%)
3		-	22%
4		**3.22**	72% (72%)

Table 3.19: Amination of Benzonitrile

Although butylamine showed the highest conversions, pyrrolidine which was also a very effective nucleophile produced cleaner reactions, this nucleophile was therefore chosen for a further range of aromatic nitriles. Slightly higher ratios of amine were used compared with previous investigations and lower temperatures were used to help promote the nucleophilic attack of the nitrile. Table 3.20, shows the conversions into the aminated product.



Entry	Nitrile	Product ID	Conversion
1			51 %
2		**3.23**	Quantitative (80%)[a]
3			Intractable mixture
4			62%

a) Isolated Yield

Table 3.20: Pyrrolidine amination of aryl nitriles

It is apparent that the electron configuration of the nitrile species imparts a significant amount of variation in the selectivity of the reaction. The major side products seen in entries 1 and 4 are the amines formed by reduction of the nitrile without attack of the pyrrolidine. The electron rich *para*-methoxybenzonitrile, Entry 2, showed complete conversion to the aminated product suggesting that the reactivity towards the amine borane is sufficiently diminished to allow for attack by the amine before reduction of the more reactive intermediate formed.

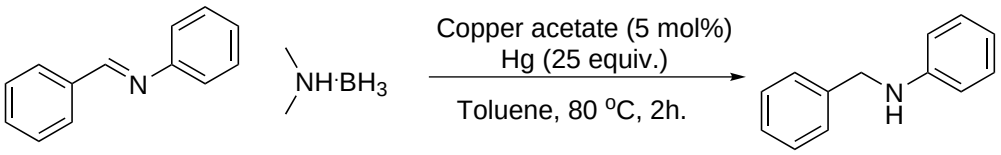
3.8 Mechanism

3.8.1 Mercury drop test

It was noticed upon running the reactions that, in the vast majority of cases, the vibrant colour associated with the copper salts in solution disappeared over time to produce a black precipitate in solution and this precipitate tended to remain until removal by filtration at the end of the reaction although after some of the longer reaction times it

was seen to degrade. The appearance of this precipitate suggested that the reaction may be proceeding through a heterogeneous pathway and so several different techniques were employed to determine the reaction mechanism. One of the most common methods for testing the phase of a catalyst is the mercury drop test whereby a large excess of elemental mercury is added to the reaction mixture. In the case of homogeneous reactions this should have little effect on the reaction rate whereas the addition of the mercury to heterogeneous reactions can lead to either coating of the catalyst surface or the formation of metal amalgams, both of which lead to significant loss of catalytic activity.

The reduction of *N*-benzylidine aniline was chosen as the reaction to determine whether the reaction proceeds through homogeneous mechanisms. This is because there is still a low background rate in the absence of catalyst however it is much lower than the rate of conversion seen in the presence of a catalyst. It was decided to form the precipitate *in situ* first, prior to the introduction of the mercury and then mix the two fully before later addition of the substrate. The results shown in Table 3.21, show that the addition of mercury reduced the conversion of the reaction down to the rate seen when no catalyst had been added. This result indicated that the reaction is heterogeneous in nature as the mercury would be expected to interact with any metal particulates formed yet not significantly interfere with a homogeneous reaction mixture.



Entry	Catalyst system	Conversion to product [a]
1	Just $(CuOAc)_2$	88%
2	$(CuOAc)_2$ plus Hg	22%
3	Neither $(CuOAc)_2$ or Hg	22%

a) Conversion as determined by ^{1}H NMR

Table 3.21: Mercury drop experiment

3.8.2 NMR studies

In order to further elucidate the phase of the catalyst, NMR studies were conducted to follow the conversion of one of the reactions over times. For homogeneous reactions there is not expected to be an incubation period and the reaction should proceed at its greatest rate from near the point of addition of the catalyst. Heterogeneous reactions,

by contrast, invariably see an induction period followed by a period of rapid conversion which tails off to produce a signature sigmoidal reaction profile.

^{1}H spectra were taken every minute to investigate the copper(II) triflate catalysed reduction of 4-nitrotoluene with dimethylamine borane in deuterated water. The results are displayed in the graph in Fig. 3.16 and they show an interesting pathway. There is an initial delay as expected for a reaction proceeding through a heterogeneous pathway, this is followed by conversion of the starting aryl nitro group into an intermediate which is postulated to be either the corresponding *N*-4-methylphenylhydroxylamine or the nitroso compound. This intermediate is then rapidly reduced to the anilinic species followed by further rapid reduction of the remaining starting nitro group.

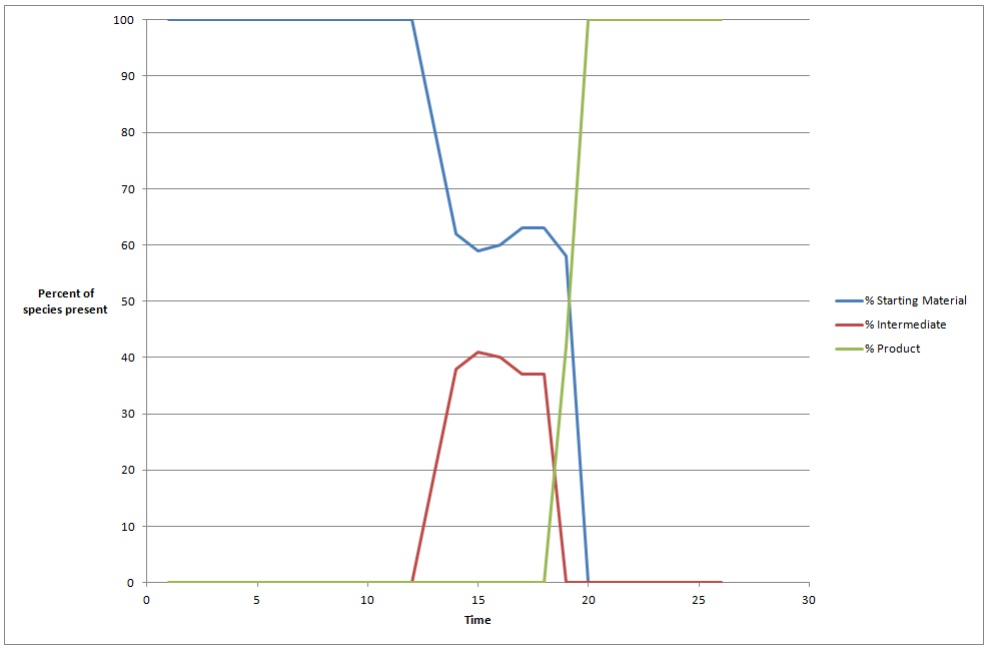


Figure 3.16: Kinetic NMR experiment for the reduction of 4-nitrotoluene

The conversions seen can only be treated as approximations due to the incomplete solubility of all the reagents and products and, although it is representative, this can explain the slightly unexpected ratios of intermediate relative to starting material around 15 minutes after the addition of the reactants.

3.9 Conclusions

It has been shown that the use of a variety of copper salts as well as elemental copper and its oxides can be used to catalyse the dehydrogenation of a range of amine boranes with dimethylamine borane showing high levels of reactivity to the catalyst. These

catalysts can be used reduce a range of organic functional groups in good conversions and under milder reaction conditions compared with some of those previously reported. Copper triflate proved the most versatile catalyst and was seen to reduce several groups chemoselectively and of particular note was the reduction of a range of alkynes selectively to the corresponding *cis*-alkenes.

The reaction was believed to proceeding through a heterogeneous mechanism which was postulated due to appearance of visible copper deposits with simultaneous decolourisation of the characteristically vivid copper solutions. The heterogeneous reaction mechanism hypothesis was supported by two separate analytical methods; the first focussing on the addition of elemental mercury led to a poisoning of the reaction which would not be expected for a homogeneous reaction. The second supporting piece of evidence focussed on the reaction kinetics which showed the existence of an induction period which is indicative of formation of the metal particulates.

Attempts to reduce aliphatic nitro groups have been attempted but whilst the reactions reached complete conversion from the starting material there were considerable amounts of side products noted, believed to be due to the presence of α-hydrogens. The reductive amination of some nitriles with highly nucleophilic amines was attempted and although the amination to form both secondary and tertiary amines was successful there were, in some cases, large amounts of side products formed reducing the conversions to the desired products.

Chapter 4

Experimental

4.1 General Experimental

All reactions with the exception of aminolysis reactions were conducted in air filled oven dried Radleys carousel tubes. The aminolysis reactions were all conducted under bottled argon in Youngs ampoules. Anhydrous acetonitrile, toluene, dichloromethane, tetrahydrofuran and diethyl ether were obtained from an Innovative Technology inc, PS-400-7 solvent purification system. Anhydrous dioxane, cyclohexane and heptane were purchased from Acros and stored over molecular sieves under argon. Petrol refers to the fraction of petroleum ether that boils between 40-60 °C. Ammonium thiocyanate was dried prior to use in an oven at 70 °C overnight, all other commercially available compounds were used as obtained from the chemical suppliers; Sigma Aldrich, Strem, Acros, Alpha Aesar and Manchester Organics. Thin Layer Chromatography (TLC) was performed using commercially available polyester backed neutral silica DC-Fertigfolien Polygram Sil G/UV_{254} plates. These were visualised under UV light (254 nm) and by staining with phosphomolybdic acid followed by heating or with ceric ammonium molybdate followed by gentle heating. Flash chromatography was performed using chromatography grade silica, 60 Å particle size 200-400 mesh from Sigma Aldrich. Organic fractions were frequently dried over $MgSO_4$ or Na_2SO_4 and concentrated *in vacuo*.

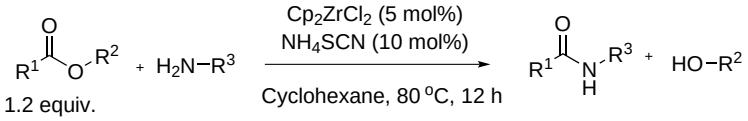
NMR samples were dissolved in $CDCl_3$, d^6-DMSO, d^3-MeCN or d^8-toluene. ^1H spectra were recorded at either 500 MHz, 300 MHz or 250 MHz whilst the $^{13}C\{^1H\}$ spectra were recorded at 125 MHz or 75 MHz on a Brüker Avance 500 or Brüker Avance 300 respectively. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to tetramethyl silane (δ=0.00 ppm). The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet; br, broad. Coupling constants (J) are quoted to the nearest 0.1 Hz. Infra red spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer with selected absorbances reported as

υ in cm^{-1}. High resolution mass spectrometry was conducted with a Brüker Daltonics microTOF spectrometer with an electrospray source and external calibrant with the samples introduced by flow injection and masses recorded in positive electrospray ionisation mode. Masses were accurate to 5 ppm and data processed using software from Brüker Daltonics. Compounds marked with a * are commercially available through Sigma Aldrich and the data collected matches the data reported.

4.2 Experimental Section for Chapter I

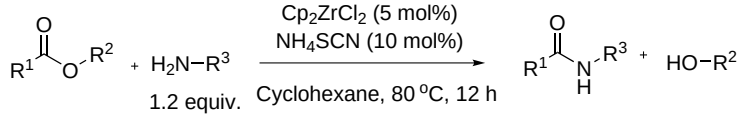
4.2.1 General Procedures

4.2.1.1 Aminolysis with an excess of ester; procedure (I)



To an oven dried, argon purged Youngs ampoule containing zirconocene dichloride (0.044 g, 0.15 mmol) was added oven dried ammonium thiocyanate (0.023 g, 0.3 mmol). The solids were mixed together under a stream of argon at 100 °C for 15 mins at which point the temperature was lowered to 80 °C and 1.5 mL of cyclohexane was added followed by ester (3.6 mmol). The suspension was mixed for a further 15 mins at which point amine was added (3.0 mmol), the tubes were sealed and the mixture allowed to react for a further 12 h at 80 °C. Upon completion the reaction mixtures were concentrated *in vacuo,* diluted with DCM (30 mL) and washed thrice with brine and NH_4Cl solution (30 mL). The organic layer was collected, dried over $MgSO_4$, filtered and reduced *in vacuo* to give the crude product which was purified by flash column chromatography in a gradated mixture of pentanes and ethyl acetate to yield the product.

4.2.1.2 Aminolysis with an excess of amine; procedure (II)

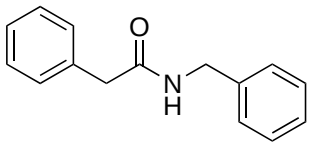


To an oven dried, argon purged Youngs ampoule containing zirconocene dichloride (0.044 g, 0.15 mmol) was added oven dried ammonium thiocyanate (0.023 g, 0.3 mmol). The solids were mixed together under a stream of argon at 100 °C for 15 mins at which point the temperature was lowered to 80 °C and 1.5 mL of cyclohexane was added followed

by ester (3.0 mmol). The suspension was mixed for a further 15 mins at which point amine was added (3.6 mmol) and the tubes sealed and the mixture allowed to react for a further 12 h at 80 °C. Upon completion the reaction mixtures were concentrated *in vacuo,* diluted with DCM (30 mL) and washed thrice with brine and HCl (1M) solution (30 mL). The organic layer was collected, dried over $MgSO_4$, filtered and reduced *in vacuo* to give the crude product which was purified by flash column chromatography in a gradated mixture of pentanes and ethyl acetate to yield the product.

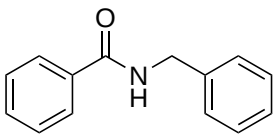
4.2.2 Amides formed by aminolysis.

1.1 *N*-Benzyl-*2*-phenylacetamide:



The title compound was formed following representative procedure II. Methyl phenyl acetate (0.42 mL, 3.0 mmol) was used as the ester species to which benzylamine (0.39 mL, 3.6 mmol) was added. A ^{1}H NMR showing 82% conversion to **1.1** was recorded. The compound was purified to give a yellow powder in a 0.487 g (72%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.56 (2H, s, Ph-C$\underline{H}_2$-C(O)), 4.33-4.38 (2H, d, J = 6.0 Hz, Ph-C$\underline{H}_2$-NH), 5.68 (1H, br, C(O)-N$\underline{H}$-CH_2), 7.09-7.12 (2H, dd, J = 1.8 Hz, aromatic), 7.17-7.31 (8H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 43.60, 43.83, 127.48, 127.51, 128.69, 129.11, 129.50, 138.10, 170.95. ESI -MS of $[C_{15}H_{15}NO]^+$; theoretical m/z of $[M+H]^+$ = 226.123, measured m/z of $[M+H]^+$ = 226.123, IR: υ = 1637.40 (C=O stretch). Consistent with the literature data.**[155]**

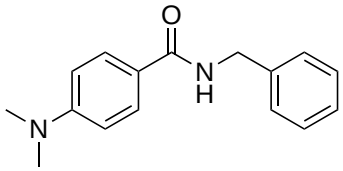
1.2 *N*-Benzylbenzamide:



The title compound was formed following representative procedure II. Ethyl benzoate (0.43 mL, 3.0 mmol) was used as the ester species to which benzylamine (0.39 mL,

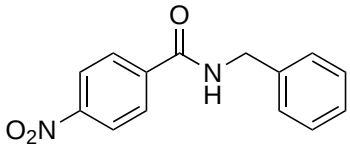
3.6 mmol) was added. A ^{1}H NMR showing 80% conversion to **1.2** was recorded. The compound was purified to give a white solid in a 0.479 g (78%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.61 (2H, d, J = 5.1 Hz, Ph-C<u>H</u>$_2$-NH), 6.71 (1H, br, C(O)-N<u>H</u>-CH_2), 7.26-7.49 (8H, m, aromatic), 7.78-7.80 (2H, d, J = 6.9, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 44.10, 127.05, 127.59, 127.90, 128.59, 128.78, 131.56, 134.37, 138.27, 167.48. ESI -MS of $[C_{14}H_{13}N\ O]^+$; theoretical m/z of $[M+H]^+$ = 212.108, measured m/z of $[M+H]^+$ = 212.109, IR: υ = 1636.74 (C=O stretch). Consistent with the literature data.**[47]**

1.3 *N*-Benzyl-(4-*N*,*N*-dimethylamino)benzamide:



The title compound was formed following representative procedure II. Ethyl-4-dimethyl aminobenzoate (0.580 g, 3.0 mmol) was used as the ester species to which benzylamine (0.39 mL, 3.6 mmol) was added. A ^{1}H NMR showing 71% conversion to **1.3** was recorded. The compound was purified to give a white powder in a 0.424 g (56%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.02 (6H, s, (C<u>H</u>$_3$)$_2$N-Ar), (2H, d, J = 5.7 Hz, Ph-C<u>H</u>$_2$-NH), 6.32 (1H, br, C(O)-N<u>H</u>-CH_2), 6.74 (2H, d, J = 8.1 Hz, aromatic), 7.28-7.36 (5H, m, aromatic), 7.72 (2H, d, J= 9.0 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 40.69, 43.98, 127.47, 127.93, 128.54, 128.73, 138.73, 167.11. ESI -MS of $[C_{16}H_{18}N_2O]^+$; theoretical m/z of $[M+H]^+$ = 277.132, measured m/z of $[M+H]^+$ = 277.132, IR: υ = 1621.70 (C=O stretch). Consistent with the literature data.**[155]**

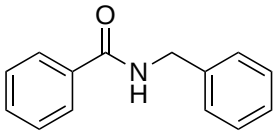
1.4 *N*-Benzyl-4-nitrobenzamide:



The title compound was formed following representative procedure II. Ethyl-4-nitro benzoate (0.586 g, 3.0 mmol) was used as the ester species to which benzylamine (0.39 mL, 3.6 mmol) was added. A ^{1}H NMR showing 93% conversion to **1.4** was recorded.

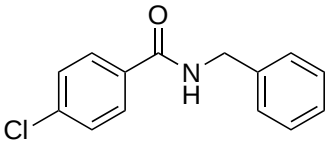
The compound was purified to give a white powder in a 0.708 g (92%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.66 (2H, d, J = 5.7 Hz, Ph-C$\underline{H}_2$-NH), 6.52 (1H, br, C(O)-N$\underline{H}$-CH_2), 7.29-7.41 (5H, m, aromatic), 7.94 (2H, d, J = 9.0 Hz, aromatic), 8.27 (2H, d, J = 9.0 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 44.52, 123.89, 128.01, 128.06, 128.20, 128.98, 137.42, 139.92, 165.31. ESI -MS of $[C_{14}H_{12}N_2O_3]^+$; theoretical m/z of $[M+H]^+$ = 257.092, measured m/z of $[M+H]^+$ = 257.091, IR: υ = 1627.30 (C=O stretch). Consistent with the literature data.**[155]**

1.5 *N*-Benzylbenzamide:



The title compound was formed following representative procedure II. Benzyl benzoate (0.570 mL, 3.0 mmol) was used as the ester species to which benzylamine (0.39 mL, 3.6 mmol) was added. A ^{1}H NMR showing 79% conversion to **1.5** was recorded. The compound was purified to give a white crystalline powder in a 0.496 g (77%) yield. ^{1}H NMR (250 MHz, $CDCl_3$) δ = 4.68 (2H, d, J = 5.8 Hz, Ph-C$\underline{H}_2$-NH), 6.45 (1H, br, C(O)-N$\underline{H}$-CH_2), 7.31-7.57 (8H, m, aromatic), 7.81-7.86 (2H, dt, J = 9.3 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 44.17, 126.96, 127.67, 127.96, 128.62, 128.82, 131.58, 138.38, 167.34. ESI -MS of $[C_{14}H_{13}NO]^+$; theoretical m/z of $[M+H]^+$ = 234.089, measured m/z of $[M+H]^+$ = 234.090, IR: υ = 1634.63 (C=O stretch). Consistent with the literature data.**[47]**

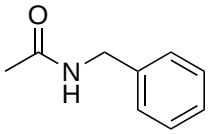
1.6 *N*-Benzyl-4-chlorobenzamide:



The title compound was formed following representative procedure II. Methyl-4-chlorobenzoate (0.512 g, 3.0 mmol) was used as the ester species to which benzylamine (0.39 mL, 3.6 mmol) was added. A ^{1}H NMR showing quantitative conversion to **1.6** was recorded. The compound was purified to give a yellow crystals in a 0.548 g (75%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.61 (2H, d, J = 5.7 Hz, Ph-C$\underline{H}_2$-NH), 6.52 (1H, br,

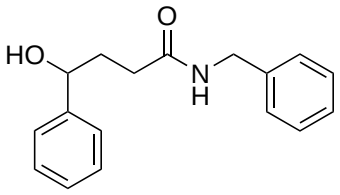
C(O)-N<u>H</u>-CH_2), 7.26-7.39 (8H, m, aromatic), 7.70-7.74 (2H, dt, J = 8.4 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 44.24, 127.76, 127.96, 128.45, 128.86, 132.70, 137.83, 137.94, 166.36. ESI -MS of $[C_{14}H_{12}NOCl]^+$; theoretical m/z of $[M+H]^+$ = 246.068, measured m/z of $[M+H]^+$ = 246.068, IR: υ = 1638.11 (C=O stretch). Consistent with the literature data.**[155]**

1.7 *N*-Benzyl acetate:



The title compound was formed following representative procedure II. *Tert*-butyl acetate (0.402 mL, 3.0 mmol) was used as the ester species to which benzylamine (0.39 mL, 3.6 mmol) was added. The reaction was allowed to proceed for 24 h in this instance and then worked up as described in the representative procedure. A ^{1}H NMR showing moderate conversion to **1.7** was recorded. The compound was purified to give a white solid in a 0.193 g (46%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.95 (3H, s, <u>H</u>$_3$C-C(O)-NH), 4.35 (2H, d, J = 5.4 Hz, Ph-C<u>H</u>$_2$-NH), 5.92 (1H, br, C(O)-N<u>H</u>-CH_2), 7.18-7.30 (5H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 23.22, 43.81, 127.60, 127.89, 128.75, 138.11, 170.12. ESI -MS of $[C_9H_{11}NO]^+$; theoretical m/z of $[M+H]^+$ = 150.092, measured m/z of $[M+H]^+$ = 150.094, IR: υ = 1650.46 (C=O stretch). Consistent with the literature data.**[47]**

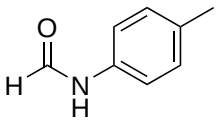
1.8 *N*-Benzyl-4-hydroxy-4-phenylbutanamide:



The title compound was formed following representative procedure II. 4-Phenyl-γ-butyrolactone (0.487 g, 3.0 mmol) was used as the ester species to which benzylamine (0.33 mL, 3.2 mmol) was added. A ^{1}H NMR showing quantitative conversion to **1.8** was recorded. The compound was purified to give a white solid in a 0.714 g (88%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.90-2.05 (2H, m, CH-C<u>H</u>$_2$-CH_2), 2.24 (2H, t, J

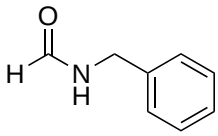
= 6.9 Hz, CH_2-C<u>H</u>$_2$-C(O)), 3.62 (1H, br,-O<u>H</u>), 4.31 (2H, d, J = 5.7 Hz, Ph-C<u>H</u>$_2$-NH), 4.65 (1H, m, C<u>H</u>-OH), 6.11 (1H, br, C(O)-N<u>H</u>-CH_2), 7.13-7.32 (10H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 32.87, 34.35, 43.78, 125.75, 127.40, 127.61, 127.85, 128.45, 128.76, 138.04, 144.41, 173.48. ESI -MS of $[C_{17}H_{19}NO_2]^+$; theoretical m/z of $[M+H]^+$ = 270.149, measured m/z of $[M+H]^+$ = 270.148, IR: υ = 1644.13 (C=O stretch).

1.9 *N*-Formyltoluidine:



The title compound was formed following representative procedure II. Butyl formate (0.343 mL, 3 mmol) was used as the ester species to which 4-methylaniline (0.321 g, 3.0 mmol) was added. A ^{1}H NMR showing quantitative conversion to **1.09** was recorded. The compound was purified by recrystallisation from ethyl acetate to give a white crystalline solid in a 0.373 g (92%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.23-2.34 (3H total, two singlets, C<u>H</u>$_3$-Ph), 6.97 (1H, d, J = 8.5 Hz, aromatic), 7.10-7.18 (2H, m, aromatic), 7.26 (1H, br s, C(O)C-N<u>H</u>), 7.42 (H, d, J = 8.4 Hz, aromatic), 8.36 (0.45, br s, C(O)<u>H</u>), 8.62 (0.45H, d, J = 11.1 Hz, C(O)<u>H</u>). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 20.85, 119.32, 119.97, 129.64, 130.31, 158.76, 162.38. ESI -MS of $[C_8H_9NO]^+$; theoretical m/z of $[M+H]^+$ = 136.076, measured m/z of $[M+H]^+$ = 136.078, IR: υ =1665.90 (C=O stretch). Consistent with the literature data.**[58]**

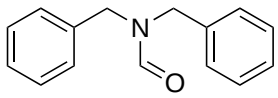
1.10 *N*-Formylbenzylamine:



The title compound was formed following representative procedure II. Butyl formate (0.343 mL, 3.0 mmol) was used as the acylating species to which benzylamine (0.39 mL, 3.6 mmol) was added. A ^{1}H NMR showing quantitative conversion to **1.10** was recorded. The compound was purified to give a yellow solid in a 0.448 g (99%) yield. The compound was isolated in a mixture of rotamers, ^{1}H NMR (300 MHz, $CDCl_3$), Mixture of rotamers seen. Ratio 4:1 Major Rotamer: δ = 4.47 (2H, d, J = 6.0 Hz, Ph-C<u>H</u>$_2$-NH), 6.05 (1H, br, C(O)-N<u>H</u>-CH_2), 7.23-7.37 (5H, m, aromatic), 8.24 (1H, s, C(O)<u>H</u>). Minor

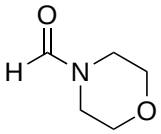
rotamer: δ = 4.40 (2H, d, J = 6.3 Hz, Ph-C$\underline{H}_2$-NH), 6.05 (1H, br, C(O)-N$\underline{H}$-CH_2), 7.23-7.37 (5H, m, aromatic), 8.16 (1H, d, J = 12.0 Hz, C(O)$\underline{H}$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 42.22, 126.99, 127.74, 127.83, 128.01, 128.82, 128.96, 137.53, 161.10. ESI -MS of $[C_8H_9NO]^+$; theoretical m/z of $[M+H]^+$ = 136.076, measured m/z of $[M+H]^+$ = 136.076, IR: υ =1650.59 (C=O stretch). Consistent with the literature data.**[156]**

1.11 *N*-Formyldibenzylamine:



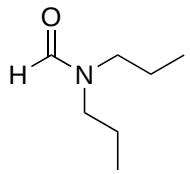
The title compound was formed following representative procedure I. Butyl formate (0.412 mL, 3.6 mmol) was used as the ester species to which dibenzylamine (0.58 mL, 3.0 mmol) was added. The compound was purified to give a golden solid in a 0.678 g (99%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.26 (2H, s, Ph-C$\underline{H}_2$-N), 4.41 (2H, s, Ph-C$\underline{H}_2$-N), 7.13-7.41 (10H, m aromatic), 8.40 (1H, s, C(O)$\underline{H}$), ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 44.64, 50.27, 127.27, 128.18, 128.54, 128.73, 128.96, 129.11, 130.42, 135.65, 136.01, 162.88. IR: υ =1670.30 (C=O stretch). Consistent with the literature data.**[156]**

1.12 *N*-Formylmorpholine:



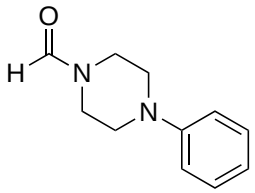
The title compound was formed following representative procedure I. Butyl formate (0.412 mL, 3.6 mmol) was used as the ester species to which morpholine (0.262 mL, 3.0 mmol) was added. The compound was purified to give a yellow liquid in a 0.170 g (50%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.33 (2H, t, J = 4.8 Hz, N-C$\underline{H}_2$-CH_2), 3.49 (2H, t, J = 4.2 Hz, N-C$\underline{H}_2$-CH_2), 3.60 (4H, m, O(-C$\underline{H}_2$-CH_2)$_2$), 7.98 (1H, s, C(O)$\underline{H}$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 40.56, 45.77, 66.37, 67.37, 160.90. ESI -MS of $[C_5H_9NO_2]^+$; theoretical m/z of $[M+H]^+$ = 138.053, measured m/z of $[M+H]^+$ = 138.055, IR: υ =1651.34 (C=O stretch). Consistent with the literature data.**[156]**

1.13 *N*-Formyl-dipropylamine:



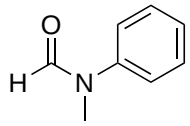
The title compound was formed following representative procedure I. Butyl formate (0.412 mL, 3.6 mmol) was used as the ester species to which dipropylamine (0.411 mL, 3.0 mmol) was added. The compound was purified to give a yellow liquid with a 0.234 g (60%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.83 (6H, dt, J = 2.7 Hz, J = 7.5 Hz, C$\underline{H}_3$-CH_2-), 1.44-1.57 (4H, m, CH_3-C$\underline{H}_2$-CH_2), 3.11 (2H, t, J = 7.2 Hz, CH_2-C$\underline{H}_2$-N), 3.19 (2H, t, J = 7.5 Hz, CH_2-C$\underline{H}_2$-N), 8.0 (1H, s, C(O)$\underline{H}$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 10.94, 11.33, 20.52, 21.81, 43.86, 49.30, 162.94. ESI -MS of $[C_7H_{15}NO]^+$; theoretical m/z of $[M+H]^+$ = 130.123, measured m/z of $[M+H]^+$ = 130.125, IR: υ =1661.70 (C=O stretch). Consistent with the literature data.**[156]**

1.14 4-Formyl-1-phenyl piperazine:



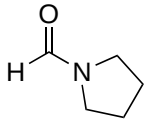
The title compound was formed following representative procedure I. Butyl formate (0.412 mL, 3.6 mmol) was used as the ester species to which 1-phenyl piperazine (0.458 mL, 3.0 mmol) was added. The compound was purified to give a golden solid in a 0.378 g (62%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.19 (4H, m, CH_2-C$\underline{H}_2$-N), 3.61 (2H, br t, CH_2-C$\underline{H}_2$-N), 3.78 (2H, br, t, CH_2-C$\underline{H}_2$-N), 6.97-7.05 (3H, m, aromatic), 7.35 (2H, t, J = 7.5 Hz, aromatic), 8.11 (1H, s, C(O)H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 39.64, 45.21, 117.60, 129.48, 160.74. ESI -MS of $[C_{11}H_{14}N_2O]^+$; theoretical m/z of $[M+H]^+$ = 191.118, measured m/z of $[M+H]^+$ = 191.119, IR: υ =1652.04 (C=O stretch). Consistent with the literature data.**[92]**

1.15 *N*-Formyl-1-methylaniline:



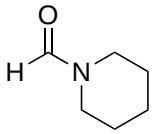
The title compound was formed following representative procedure I. Butyl formate (0.412 mL, 3.6 mmol) was used as the ester species to which 1-methylaniline (0.325 mL, 3.0 mmol) was added. The compound was purified to give a yellow liquid in a 0.366 g (95%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.29 (3H, s, N-C$\underline{H}_3$), 7.14 (2H, d, J = 8.1 Hz, aromatic), 7.22-7.25 (1H, m, aromatic), 7.39 (2H, t, J = 8.1 Hz, aromatic), 8.45 (1H, s, C(O)$\underline{H}$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 32.07, 122.36, 126.43, 129.64, 142.16, 162.39. ESI -MS of $[C_8H_9NO]^+$; theoretical m/z of $[M+H]^+$ =158.058, measured m/z of $[M+H]^+$ = 158.059, IR: υ =1666.96 (C=O stretch). Consistent with the literature data.**[57]**

1.16 *N*-Formylpyrrolidine:



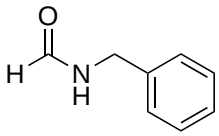
The title compound was formed following representative procedure I. Butyl formate (0.412 mL, 3.6 mmol) was used as the ester species to which pyrrolidine (0.250 mL, 3.0 mmol) was added. The compound was purified to give a yellow liquid in a 0.156 g (52%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.79 (4H, m, N-(CH_2-C$\underline{H}_2$)$_2$), 3.29 (2H, t, J = 6.9 Hz, N-(C$\underline{H}_2$-CH_2)$_2$), 3.38 (2H, t, J = 6.9 Hz, N-(C$\underline{H}_2$-CH_2)$_2$), 8.13 (1H, s, C(O)$\underline{H}$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 24.13, 24.80, 43.06, 45.99, 160.87. ESI -MS of $[C_5H_9NO]^+$; theoretical m/z of $[M+H]^+$ = 100.0762, measured m/z of $[M+H]^+$ = 100.076, IR: υ =1643.60 (C=O stretch). Consistent with the literature data.**[156]**

1.17 *N*-Formylpiperidine:



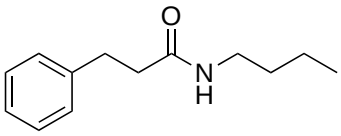
The title compound was formed following representative procedure I. Butyl formate (0.412 mL, 3.6 mmol) was used as the ester species to which piperidine (0.296 mL, 3.0 mmol) was added. The compound was purified to give a yellow liquid with a 0.292 g (86%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.44 (4H, m, CH_2-C$\underline{H}_2$-CH_2), 1.58 (2H, m, CH_2-C$\underline{H}_2$-CH_2), 3.21 (2H, t, J = 5.4 Hz CH_2-C$\underline{H}_2$-N), 3.37 (2H, t, J = 5.4 Hz CH_2-C$\underline{H}_2$-N), 7.89 (1H, s, C(O)$\underline{H}$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 24.62, 25.02, 26.51, 40.56, 46.80, 160.81. ESI -MS of $[C_6H_{11}NO]^+$; theoretical m/z of $[M+H]^+$ = 136.074, measured m/z of $[M+H]^+$ = 136.076, IR: υ =1654.48 (C=O stretch). Consistent with the literature data.**[156]**

1.18 *N*-Benzylformamide:



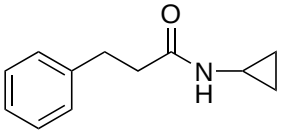
The title compound was formed following representative procedure II with the alteration that the temperature was lowered to 55 °C once the solids had been purged, the reaction was allowed to run for 24 h. Ethyl formate (0.241 mL, 3.0 mmol) was used as the ester species to which benzylamine (0.393 mL, 3.6 mmol) was added. The compound was purified to give a yellow solid in a 0.396 g (88%) yield .The compound was isolated in a mixture of rotamers, ^{1}H NMR (300 MHz, $CDCl_3$), Mixture of rotamers seen. Ratio 5:1 Major rotamer: δ = 4.49 (2H, d, J = 5.7 Hz, Ph-C$\underline{H}_2$-NH), 5.99 (1H, br, C(O)-N$\underline{H}$-CH_2), 7.24-7.41 (5H, m, aromatic), 8.27 (1H, s, C(O)$\underline{H}$). Minor rotamer: δ = 4.42 (2H, d, J = 6.3 Hz, Ph-C$\underline{H}_2$-NH), 5.99 (1H, br, C(O)-N$\underline{H}$-CH_2), 7.24-7.41 (5H, m, aromatic), 8.18 (1H, d, J = 12.0 Hz, C(O)$\underline{H}$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 42.28, 127.78, 127.86, 128.84, 161.08. ESI -MS of $[C_8H_9NO]^+$; theoretical m/z of $[M+H]^+$ = 136.076, measured m/z of $[M+H]^+$ = 136.076, IR: υ =1637.45 (C=O stretch). Consistent with the literature data.**[156]**

1.19 *N*-Butyl-3-phenylpropanamide:



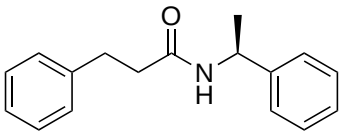
The title compound was formed following representative procedure I. Ethylhydrocinnamate (0.654 mL, 3.6 mmol) was used as the ester species to which butylamine (0.297 mL, 3.0 mmol) was added. The compound was purified to give a yellow liquid in a 0.512 g (83%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.80 (3H, t, J = 7.2 Hz, $C\underline{H}_3$-CH_2-CH_2), 1.16 (2H, m, CH_3-$C\underline{H}_2$-CH_2), 1.32 (2H, m, CH_3-CH_2-$C\underline{H}_2$-), 2.39 (2H, t, J = 7.2 Hz, CH_2-$C\underline{H}_2$-C(O)), 2.88 (2H, t, J = 7.5 Hz, Ph-$C\underline{H}_2$-CH_2-), 3.11 (2H, q, J = 6.0 Hz, NH-$C\underline{H}_2$-CH_2-), 5.65 (1H, br, C(O)-N$\underline{H}$-CH_2), 7.04-7.22 (5H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 13.76, 20.01, 31.60, 31.86, 38.50, 39.28, 126.22, 128.36, 128.51, 140.91, 172.20. ESI -MS of $[C_{13}H_{19}NO]^+$; theoretical m/z of $[M+H]^+$ = 206.154, measured m/z of $[M+H]^+$ = 206.155, IR: υ = 1635.37 (C=O stretch). Consistent with the literature data.**[12]**

1.20 *N*-Cyclopropyl-3-phenylpropanamide:



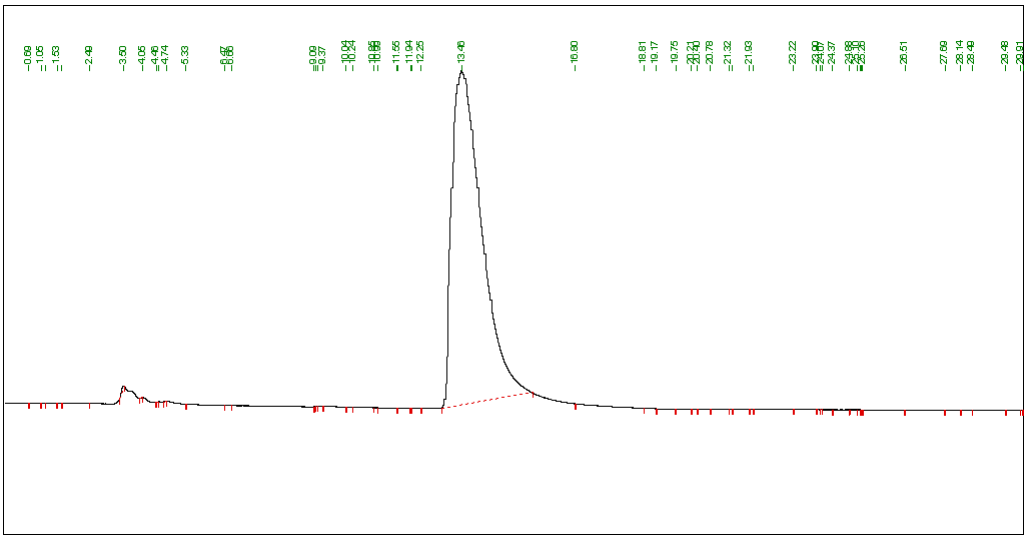
The title compound was formed following representative procedure I. Ethylhydrocinnamate (0.654 mL, 3.6 mmol) was used as the ester species to which cyclopropylamine (0.208 mL, 3.0 mmol) was added. The compound was purified by recrystallisation to give beige crystals in a 0.311 g (55%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.34 (2H, m, NH-CH-$C\underline{H}_2$-CH_2), 0.66 (2H, m, NH-CH-$C\underline{H}_2$-CH_2), 2.37 (2H, t, J = 7.5 Hz, CH_2-$C\underline{H}_2$-C(O)), 2.59 (1H, m, NH-C$\underline{H}$-CH_2-), 2.88 (2H, t, J = 7.5 Hz, Ph-$C\underline{H}_2$-CH_2-), 5.69 (1H, br, C(O)-N$\underline{H}$-CH_2), 7.10-7.24 (5H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 6.57, 22.64, 31.79, 38.24, 126.30, 128.40, 128.54, 140.74, 173.79. ESI -MS of $[C_{12}H_{15}NO]^+$; theoretical m/z of $[M+H]^+$ = 190.123, measured m/z of $[M+H]^+$ = 190.124, IR: υ =1641.39 (C=O stretch). Consistent with the literature data.**[58]**

1.21 *N*-(*S*)-α-Methylbenzyl-3-phenylpropanamide:

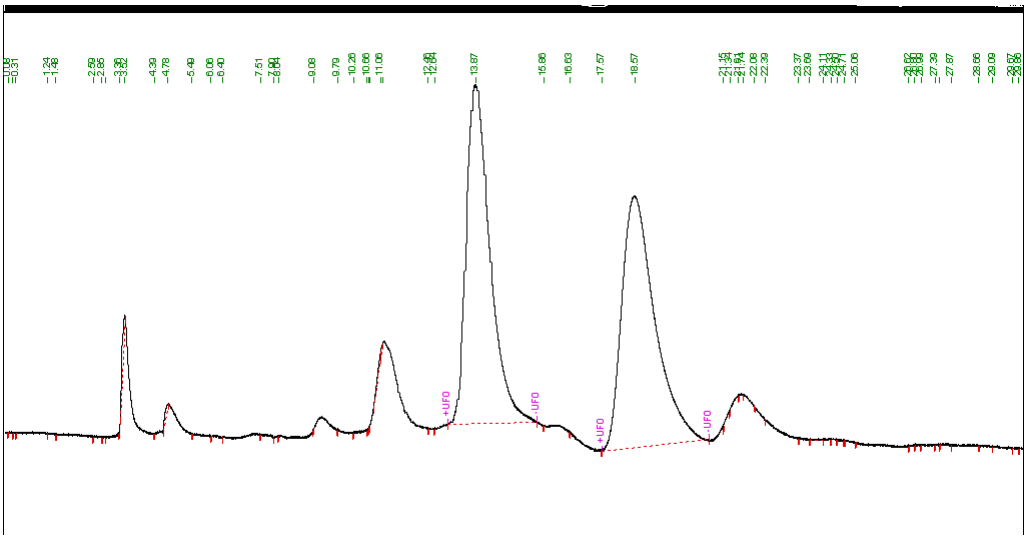


The title compound was formed following representative procedure I. Ethylhydrocinnamate (0.654 mL, 3.6 mmol) was used as the ester species to which *S*-α-methylbenzylamine (0.387 mL, 3.0 mmol) was added. The compound was purified to give white crystals in a 0.396 g (52%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.40 (3H, d J = 6.9 Hz, $C\underline{H}_3$-CH(NR)-Ph), 2.48 (2H, t, J = 7.2 Hz, CH_2-$C\underline{H}_2$-C(O)), 2.97 (2H, t, J = 7.5 Hz, Ph-$C\underline{H}_2$-CH_2-), 5.09 (1H, qu, J = 7.2 Hz, CH_3-$C\underline{H}$(NR)-Ph), 5.62 (1H, br, C(O)-N$\underline{H}$-CH_2), 7.14-7.33 (10H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 21.61, 31.76, 38.62, 48.65, 126.18, 126.28, 127.34, 128.46, 128.58, 128.65, 140.78, 143.01, 171.16. ESI -MS of $[C_{17}H_{19}NO]^+$; theoretical m/z of $[M+H]^+$ = 254.154, measured m/z of $[M+H]^+$ = 254.156, IR: υ = 1637.65 (C=O stretch). Optical rotation $[\alpha]_D^{25^oC}$= -41 (c = 0.020 g / 2 mL in $CHCl_3$). HPLC: Chiralcel AD column (25 cm), 1.0 mL/min, 90:10 Hexanes:IPA, *S*-enantiomer retention time 13.49 mins, >99.9 % ee. Consistent with the literature data. **[157]**

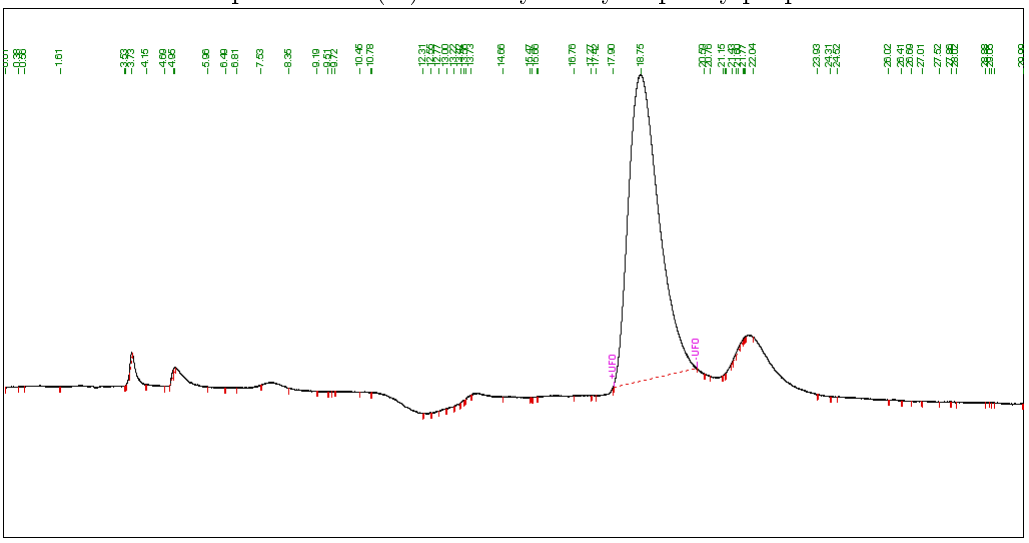
HPLC run of *N*-(*S*)-α-Methylbenzyl-3-phenylpropanamide



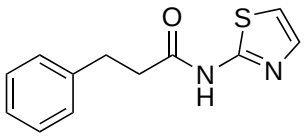
HPLC run of racemic *N*-α-Methylbenzyl-3-phenylpropanamide



HPLC run of comparative *N*-(*R*)-α-Methylbenzyl-3-phenylpropanamide



1.22 *N*-2-Amino-thiazoyl-3-phenylpropanamide:



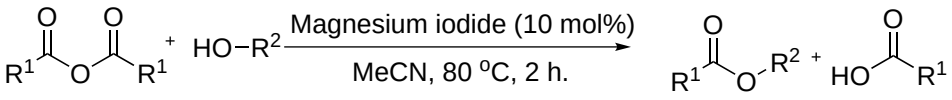
The title compound was formed following representative procedure I. Ethylhydrocinnamate (0.654 mL, 3.6 mmol) was used as the ester species to which 2-aminothiazole (0.300 g, 3.0 mmol) was added. The compound was purified to give a yellow powder in a

0.302 g (44%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.86 (2H, t, J = 7.5 Hz, CH_2-C<u>H</u>$_2$-C(O)), 3.10 (2H, t, J = 7.8 Hz, Ph-C<u>H</u>$_2$-CH_2-), 6.98 (1H, d, J = 3.6 Hz, S-C<u>H</u>-CH), 7.16-7.32 (6H, m, aromatic and N<u>H</u>), 7.34 (1H, d, J = 3.6 Hz, N-C<u>H</u>-CH-). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 30.96, 37.88, 113.62, 126.50, 128.28, 128.70, 135.72, 140.16, 160.04, 170.32. ESI -MS of $[C_{12}H_{12}N_2OS]^+$; theoretical m/z of $[M+H]^+$ = 255.057, measured m/z of $[M+H]^+$ = 255.055, IR: υ =1688.03 (C=O stretch).

4.3 Experimental Section for Chapter II

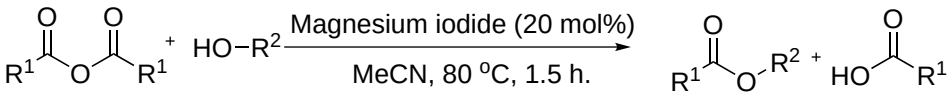
4.3.1 General procedures

4.3.1.1 General procedure for the acylation of a alcohol with an acid anhydride; procedure (III)



To an oven dried Radleys tube was added magnesium iodide (0.0834 mg, 0.3 mmol) followed by acid anhydride (3.3 mmol) then alcohol (3.0 mmol). Acetonitrile (3 mL), stored over molecular sieves, was introduced and the tubes sealed. The reactions were heated just under reflux at 80 °C for 2 h. After this time the reactions were briefly allowed to cool, diluted with DCM (25 mL) and separated with; $Na_2S_2O_3$ (10 mL), NaOH (2M, 10 mL) and brine (20 mL). The organic layer was collected and the aqueous layer washed twice more with DCM (10mL), all of the organic layers were collected, dried over $MgSO_4$, filtered and reduced *in vacuo* to give the crude product which was columned in a gradated mixture of pentanes and ethyl acetate to yield the product.

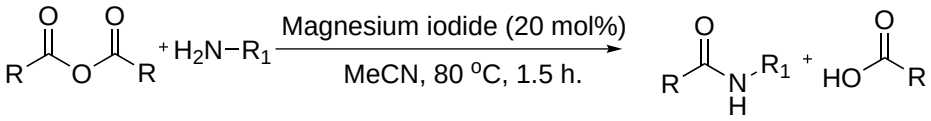
4.3.1.2 General procedure for the acylation of a alcohol with a challenging acid anhydride; procedure (IV)



To an oven dried Radleys tube was added magnesium iodide (0.167 g, 0.6 mmol) followed by acid anhydride (3.3 mmol) then alcohol (3.0 mmol). Acetonitrile (3 mL), stored over molecular sieves, was introduced and the tubes sealed. The reactions were

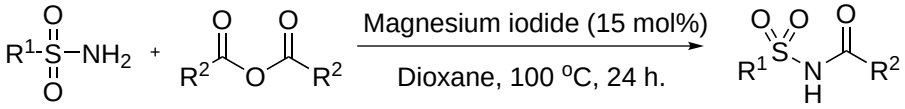
heated just under reflux at 80 °C for 1.5 h. After this time the reactions were briefly allowed to cool, diluted with DCM (25 mL) and separated with; $Na_2S_2O_3$(10 mL), NaOH (2M, 10 mL) and brine (20 mL). The organic layer was collected and the aqueous layer washed twice more with DCM (10mL), all of the organic layers were collected, dried over $MgSO_4$, filtered and reduced *in vacuo* to give the crude product which was columned in a gradated mixture of pentanes and ethyl acetate to yield the product.

4.3.1.3 General procedure for the acylation of an amine with an acid anhydride; procedure (V)



To an oven dried Radleys tube was added magnesium iodide (0.167 g, 0.6 mmol) followed by acid anhydride (3.0 mmol) then amine (3.3 mmol). Acetonitrile (3 mL), stored over molecular sieves, was introduced and the tubes sealed. The reactions were heated just under reflux at 80 °C for 1.5 h. After this time the reactions were briefly allowed to cool, diluted with ethyl acetate (25 mL) and washed with; $Na_2S_2O_3$ (10 mL) and brine (10 mL) followed by two washes with, HCl (1M, 10 mL) and brine (20 mL). The organic layer was collected, dried over $MgSO_4$, filtered and reduced *in vacuo* to give the crude product which was columned in a gradated mixture of pentanes and ethyl acetate to yield the product.

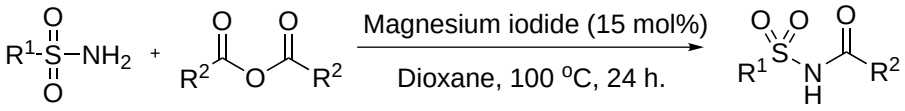
4.3.1.4 General procedure for the acylation of a sulfonamide with an acid anhydride; procedure (VI)



To an oven dried Radleys tube was added magnesium iodide (0.125 g, 0.45 mmol) followed by acid anhydride (3.3 mmol) then sulfonamide (3.0 mmol). Acetonitrile (3 mL), stored over molecular sieves, was introduced and the tubes sealed. The reactions were heated just under reflux at 80 °C for 1.5 h. After this time the reactions were briefly allowed to cool, diluted with DCM (25 mL) and separated with; $Na_2S_2O_3$ (10

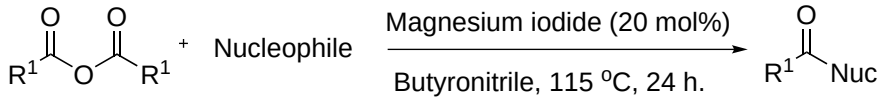
mL), NaOH (2M, 10 mL) and brine (20 mL). The organic layer was collected and the aqueous layer washed twice more with DCM (10mL), all of the organic layers were collected, dried over $MgSO_4$, filtered and reduced *in vacuo* to give the crude product which was columned in a gradated mixture of pentanes and ethyl acetate to yield the product.

4.3.1.5 General procedure for the acylation of a sulfonamide with an acid anhydride; procedure (VII)



To an oven dried Radleys tube was added magnesium iodide (0.125 g, 0.45 mmol) followed by acid anhydride (3.3 mmol) then sulfonamide (3.0 mmol). Acetonitrile (3 mL), stored over molecular sieves, was introduced and the tubes sealed. The reactions were heated just under reflux at 80 °C for 1.5 h. After this time the reactions were briefly allowed to cool, diluted with DCM (25 mL) and separated with; $Na_2S_2O_3$ (10 mL), NaOH (2M, 10 mL) and brine (20 mL). The organic layer was collected and the aqueous layer washed twice more with DCM (10mL), all of the organic layers were collected, dried over $MgSO_4$, filtered and reduced *in vacuo* to give the crude product which was purified by precipitation from ethyl acetate with slow addition of hexane to yield the product.

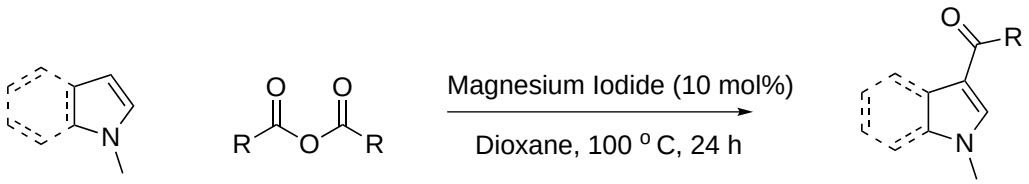
4.3.1.6 General procedure for the acylation of challenging nucleophiles with an acid anhydride; procedure (VIII)



To an oven dried Radleys tube was added magnesium iodide (0.167 g, 0.6 mmol) followed by acid anhydride (6.0 mmol) then the nucleophile (3.0 mmol). Butyronitrile (3 mL), was introduced and the tubes sealed. The reactions were heated just under reflux at 115 °C for 24 h. After this time the reactions were briefly allowed to cool, diluted with DCM (25 mL) and washed with; $Na_2S_2O_3$ (10 mL) and brine (10 mL) followed by two washes with, NaOH (2M, 10 mL) and brine (20 mL). The organic layer was collected,

dried over $MgSO_4$, filtered and reduced *in vacuo* to give the crude product which was columned in a gradated mixture of pentanes and ethyl acetate to yield the product.

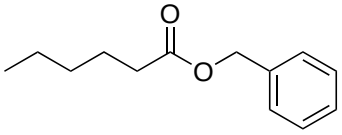
4.3.1.7 General procedure for the acylation of heterocyclic nucleophiles with an acid anhydride; procedure (IX)



To an oven dried Radleys tube was added magnesium iodide (0.167 g, 0.6 mmol) followed by acid anhydride (3.6 mmol) then the substrate (3.0 mmol). Dioxane (3 mL), was introduced and the tubes sealed. The reactions were heated just under reflux at 100 °C for 24 h. After this time the reactions were briefly allowed to cool, diluted with DCM (25 mL) and washed with; $Na_2S_2O_3$ (10 mL) and brine (3x10 mL). The organic layer was collected, dried over $MgSO_4$, filtered and reduced *in vacuo* to give the crude product which was recrystallised from ethyl acetate to yield the product.

4.3.2 Products formed from acylations with anhydrides.

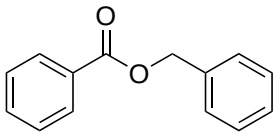
2.1 Benzyl hexanoate:*



The title compound was formed following representative procedure III. Hexanioc anhydride (0.762 mL, 3.3 mmol) was used as the acylating species to which benzyl alcohol (0.310 mL, 3.0 mmol) was added. The compound was purified to give a clear liquid in a 0.533 g (86%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.80 (3H, t, J = 7.2 Hz, C$\underline{H}_3$-CH_2-CH_2-CH_2-), 1.17-1.27 (4H, m, CH_3-C$\underline{H}_2$-C$\underline{H}_2$-CH_2-), 1.57 (2H, qu, J = 7.5 Hz, CH_3-CH_2-CH_2-C$\underline{H}_2$-), 2.27 (2H, t, J = 7.8 Hz, CH_2-C$\underline{H}_2$-C(O)O-), 5.03 (2H, s, Ph-C$\underline{H}_2$-O), 7.17-7.37 (5H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 13.95,

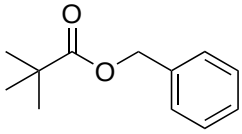
22.25, 24.68, 31.62, 33.32, 66.09, 128.20, 128.21, 128.41, 125.58, 136.16, 173.74. ESI -MS of $[C_{13}H_{18}O_2]^+$; theoretical m/z of $[M+H]^+$ = 229.120, measured m/z of $[M+H]^+$ = 229.120, IR: υ = 1734.77 (C=O stretch). Consistent with the literature data supplied from a commercial source.

2.2 Benzyl benzoate:



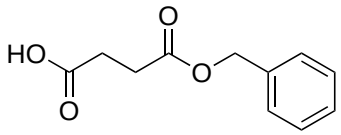
The title compound was formed following representative procedure III. Benzoic anhydride (0.747 g, 3.3 mmol) was used as the acylating species to which benzyl alcohol (0.310 mL, 3.0 mmol) was added. The compound was purified to give a clear liquid in a 0.631 g (99%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.39 (2H, s, Ph-C$\underline{H}_2$-O-), 7.28-7.63 (8H, m, aromatic), 7.10 (2H, d, J = 7.2 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 66.74, 128.22, 128.30, 128.43, 128.65, 129.75, 130.15, 133.10, 136.08, 166.49. ESI -MS of $[C_{14}H_{12}O_2]^+$; theoretical m/z of $[M+H]^+$ = 235.073, measured m/z of $[M+H]^+$ = 235.074, IR: υ = 1714.73 (C=O stretch). Consistent with the literature data.**[95]**

2.3 Benzyl trimethylacetate:



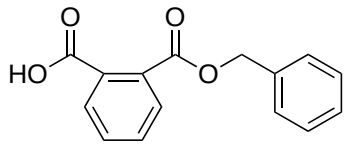
The title compound was formed following representative procedure III. Pivalic anhydride (0.669 mL, 3.3 mmol) was used as the acylating species to which benzyl alcohol (0.310 mL, 3.0 mmol) was added. The compound was purified to give a clear liquid in a 0.546 g (95%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.25 (9H, s, (C$\underline{H}_3$)$_3$C-CO-), 5.13 (2H, s, Ph-C$\underline{H}_2$-O-), 7.24-7.43 (5H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.23, 66.05, 127.71, 128.00, 128.33, 128.53, 136.49, 178.37. ESI -MS of $[C_{12}H_{16}O_2]^+$; theoretical m/z of $[M+H]^+$ = 215.105, measured m/z of $[M+H]^+$ = 215.105, IR: υ = 1727.36 (C=O stretch). Consistent with the literature data.**[111]**

2.4 Mono-benzylsuccinate:



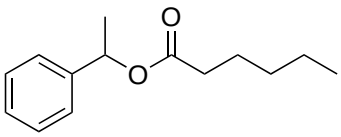
The title compound was formed following representative procedure IV. Succinic anhydride (0.33 g, 3.3 mmol) was used as the acylating species to which benzyl alcohol (0.310 mL, 3.0 mmol) was added. The compound was purified by washing with $Na_2S_2O_3$ followed by NaOH (2 M, 10 mL), The aqueous layer was taken, acidified with HCl (1M 30mL), and washed with DCM (3x 20 mL). The organic layers were collected, reduced *in vacuo* and purified by flash chromatography to give a white powder in a 0.338 g (54%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.67-2.78 (4H, m, HOOC-C$\underline{H}_2$-C$\underline{H}_2$-COO-), 5.18 (2H, s, Ph-C$\underline{H}_2$-O-), 7.33-7.45 (5H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 28.19, 29.18, 66.43, 128.32, 128.73, 135.34, 171.98, 177.30. ESI -MS of $[C_{11}H_{12}O_4]^+$; theoretical m/z of $[M+H]^+$ = 231.063, measured m/z of $[M+H]^+$ =231.062, IR: υ = 1725.83 (C=O stretch). Consistent with the literature data.**[158]**

2.5 Mono-benzylphthaloate:



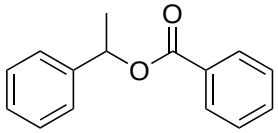
The title compound was formed following representative procedure IV. Phthalic anhydride (0.489 g, 3.3 mmol) was used as the acylating species to which benzyl alcohol (0.310 mL, 3.0 mmol) was added. The compound was purified by washing with $Na_2S_2O_3$ followed by NaOH (2 M, 10 mL), The aqueous layer was taken, acidified with HCl (1M 30 mL), and washed with DCM (3x 20 mL). The organic layers were collected, reduced *in vacuo* and purified by flash chromatography to give a white solid in a 0.338 g (54%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.36 (2H, s, Ph-C$\underline{H}_2$-O-), 7.30-8.05 (10H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 67.89, 125.74, 128.46, 128.56, 128.64, 128.99, 130.06, 131.05, 124.24, 136.05, 168.01, 171.27. ESI -MS of $[C_{15}H_{12}O_4]^+$; theoretical m/z of $[M+H]^+$ = 257.081, measured m/z of $[M+H]^+$ = 257.079, IR: υ = 1721.88 (C=O stretch).Consistent with the literature data.**[159]**

2.6 1-Phenylethyl hexanoate:*



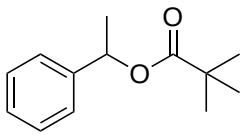
The title compound was formed following representative procedure III. Hexanoic anhydride (0762 mL, 3.3 mmol) was used as the acylating species to which 1-phenyl ethanol (0.310 mL, 3.0 mmol) was added. The compound was purified to give a yellow liquid in a 0.661 g (88%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.80 (3H, t, J = 6.9 Hz, C<u>H</u>$_3$-CH$_2$-CH$_2$-CH$_2$-), 1.14-1.28 (4H, m, CH$_3$-C<u>H</u>$_2$-C<u>H</u>$_2$-CH$_2$-), 1.45 (3H, d, J = 6.6 Hz, C<u>H</u>$_3$-CH), 1.55 (2H, qu, J = 7.5 Hz, CH$_3$-CH$_2$-CH$_2$-C<u>H</u>$_2$-), 2.24 (2H, t, J = 8.1 Hz, CH$_2$-C<u>H</u>$_2$-C(O)O-), 5.83 (1H, q, J = 6.6 Hz, Ph-C<u>H</u>-(CH$_3$)-O-), 7.17-7.29 (5H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 13.94, 22.30, 22.34, 24.68, 31.29, 34.61, 72.03, 126.08, 127.81, 128.49, 141.88, 173.13. ESI -MS of $[C_{14}H_{20}O_2]^+$; theoretical m/z of $[M+H]^+$ = 243.136, measured m/z of $[M+H]^+$ = 243.136, IR: υ = 1732.32 (C=O stretch). Consistent with the literature data supplied from a commercial source.

2.7 1-Phenylethyl benzoate:



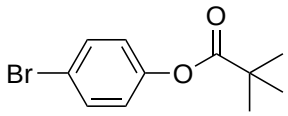
The title compound was formed following representative procedure III. Benzoic anhydride (0.747 g, 3.3 mmol) was used as the acylating species to which 1-phenyl ethanol (0.310 mL, 3.0 mmol) was added. The compound was purified to give a yellow liquid in a 0.374 g (55%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.69 (3H, d, J = 6.6 Hz, C<u>H</u>$_3$-CH), 6.17 (1H, q, J = 6.6 Hz, CH$_3$-C<u>H</u>), 7.23-7.60 (8H, m, aromatic), 8.10 (2H, d, J = 8.4 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 22.47, 72.96, 126.09, 129.35, 127.18, 127.94, 128.28, 128.38, 128.50, 128.60, 132.97, 142.82, 165.86. ESI -MS of $[C_{15}H_{14}O_2]^+$; theoretical m/z of $[M+H]^+$ = 249.089, measured m/z of $[M+H]^+$ = 249.089, IR: υ = 1713.36 (C=O stretch). Consistent with the literature data.**[118]**

2.8 1-Phenylethyl trimethylacetate:



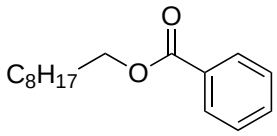
The title compound was formed following representative procedure III. Trimethylacetic anhydride (0.669 mL, 3.3 mmol) was used as the acylating species to which 1-phenyl ethanol (0.310 mL, 3.0 mmol) was added. The compound was purified to give a clear liquid with a 0.354 g (90%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.13 (9H, s, $(C\underline{H}_3)_3CC(O)$), 1.43 (3H, d, J = 6.6 Hz, $C\underline{H}_3$-CH), 5.78 (1H, q, J = 6.6 Hz, CH_3-$C\underline{H}$), 7.14-7.26 (5H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 22.46, 26.54, 38.74, 71.95, 125.80, 127.66, 128.48, 142.19, 177.67. ESI -MS of $[C_{13}H_{18}O_2]^+$; theoretical m/z of $[M+H]^+$ = 229.120, measured m/z of $[M+H]^+$ = 229.118, IR: υ = 1726.54 (C=O stretch). Consistent with the literature data.**[111]**

2.9 4-Bromophenyl trimethylacetate:



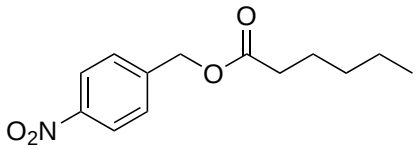
The title compound was formed following representative procedure III. Trimethylacetic anhydride (0.669 mL, 3.3 mmol) was used as the acylating species to which 4-bromophenol (0.519 g, 3.0 mmol) was added. The compound was purified to give a white solid in a 0.609 g (79%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.26 (9H, s, $(C\underline{H}_3)_3CC(O)$), 6.87 (2H, d, J = 9.0 Hz, aromatic), 7.40 (2H, d, J = 9.0 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.11, 40.21, 118.65, 123.37, 132.39, 150.15, 176.78. ESI -MS of $[C_{11}H_{13}O_2Br]^+$; theoretical m/z of $[M+H]^+$ = 279.000, measured m/z of $[M+H]^+$ = 278.997, IR: υ = 1749.72 (C=O stretch). Consistent with the literature data.**[160]**

2.10 Nonanyl benzoate:



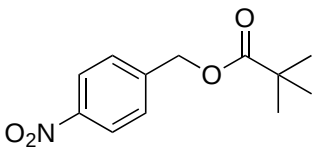
The title compound was formed following representative procedure III. Benzoic anhydride (0.747 g, 3.3 mmol) was used as the acylating species to which nonanol (0.525 mL, 3.0 mmol) was added. The compound was purified to give a yellow liquid in a 0.720g (97%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.81 (3H, t, J = 7.2 Hz, C$\underline{H}_3$-CH_2-), 1.16-1.42 (12H, m, alkyl chain), 1.69 (2H, qu, J = 8.1 Hz, -C$\underline{H}_2$-CH_2-O-), 4.24 (2H, t, J = 6.6 Hz, -CH_2-C$\underline{H}_2$-O-), 7.31-7.51 (3H, m, aromatic), 7.97 (2H, d, J = 6.9 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 14.14, 22.69, 26.07, 28.74, 29.27, 29.32, 29.62, 31.88, 65.17, 128.33, 129.55, 130.55, 132.81, 166.72. ESI -MS of $[C_{16}H_{24}O_2]^+$; theoretical m/z of $[M+H]^+$ = 249.185, measured m/z of $[M+H]^+$ = 249.184, IR: υ = 1718.70 (C=O stretch). Consistent with the literature data.**[106]**

2.11 4-Nitrobenzyl hexanoate:



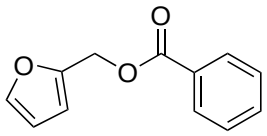
The title compound was formed following representative procedure III. Hexanoic anhydride (0.762 mL, 3.3 mmol) was used as the acylating species to which 4-nitrobenzyl alcohol (0.549 g, 3.0 mmol) was added. The compound was purified to give a clear liquid in a 0.754 g (99%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.88 (3H, t, J = 6.9 Hz, C$\underline{H}_3$-CH_2-CH_2-CH_2-), 1.30 (4H, m, CH_3-C$\underline{H}_2$-C$\underline{H}_2$-CH_2-), 1.65 (2H, qu, J = 3.9 Hz, CH_3-CH_2-CH_2-C$\underline{H}_2$-), 2.36 (2H, qu, J = 3.9 Hz, CH_2-C$\underline{H}_2$-C(O)O-), 5.20 (2H, s, Ph-C$\underline{H}_2$-O-), 7.49 ((2H, d, J = 9.0 Hz, aromatic), 8.19 (2H, d, J = 9.0 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 13.91, 22.30, 24.58, 31.21, 33.98, 64.58, 123.80, 128.34, 143.46, 147.62, 173.43. ESI -MS of $[C_{13}H_{17}NO_4]^+$; theoretical m/z of $[M+H]^+$ = 274.106, measured m/z of $[M+H]^+$ = 274.103, IR: υ = 1738.68 (C=O stretch). Consistent with the literature data.**[106]**

2.12 4-Nitrobenzyl trimethylacetate:



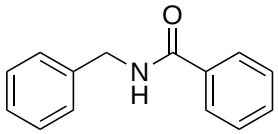
The title compound was formed following representative procedure III. Trimethylacetic anhydride (0.669 mL, 3.3 mmol) was used as the acylating species to which 4-nitrobenzyl alcohol (0.549 g, 3.0 mmol) was added. The compound was purified to give a yellow liquid in a 0.706g (99%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.24 (9H, s, (C$\underline{H}_3$)$_3$CC(O)), 5.19 (2Hs, Ph-C$\underline{H}_2$-O-), 7.50 (2H, d, J = 9.0 Hz, aromatic), 8.21 (2H, d, J = 9.0 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.16, 38.85, 64.64, 123.81, 127.98, 143.97, 147.57, 178.02. ESI -MS of $[C_{12}H_{15}NO_4]^+$; theoretical m/z of $[M+H]^+$ = 206.090, measured m/z of $[M+H]^+$ = 206.089, IR: υ = 1792.31 (C=O stretch). Consistent with the literature data.**[106]**

2.13 Furfuryl benzoate:*



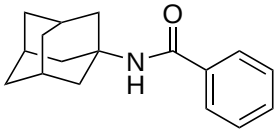
The title compound was formed following representative procedure III. Benzoic anhydride (0.747 g, 3.3 mmol) was used as the acylating species to which freshly distilled furfuryl alcohol (0.259 mL, 3.0 mmol) was added. The compound was purified to give a brown liquid in a 0.298 g (49%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.32 (2H, s, C-C$\underline{H}_2$-OC(O)), 6.36 (1H, m, C$\underline{H}$-CH-C-CH_2-O), 6.50 (1H, d, J = 3.0 Hz, CH-C$\underline{H}$-C-CH_2-O), 7.39-7.58 (4H, m , aromatic), 8.06 (2H, dd, J = 7.2 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 58.54, 110.65, 110.86, 128.92, 129.90, 133.13, 143.35, 149.56, 166.28. ESI -MS of $[C_{12}H_{10}O_3]^+$; theoretical m/z of $[M+H]^+$ = 225.053, measured m/z of $[M+H]^+$ = 225.052, IR: υ = 1716.40 (C=O stretch). Consistent with the literature data supplied from a commercial source.

2.14 *N*-Benzyl benzamide:



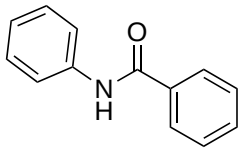
The title compound was formed following representative procedure V. Benzoic anhydride (0.679 g, 3.0 mmol) was used as the acylating species to which benzylamine (0.360 mL, 3.3 mmol) was added. The compound was purified to give white crystals in a 0.575 g (91%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.65 (2H, d, J = 5.7 Hz, Ph-CH_2NH), 7.29-7.53 (8H, m, aromatic), 7.79 (2H, dt, J = 6.6 Hz, J = 1.8 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 44.17, 126.98, 127.67, 127.96, 128.73, 128.83, 131.59, 134.39, 138.18, 167.36. ESI -MS of $[C_{14}H_{13}NO]^+$; theoretical m/z of $[M+H]^+$ = 212.108, measured m/z of $[M+H]^+$ = 212.108, IR: υ = 1634.75 (C=O stretch). Consistent with the literature data.**[47]**

2.15 *N*-Adamantyl benzamide:



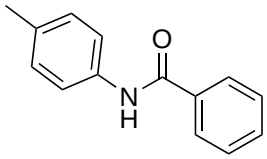
The title compound was formed following representative procedure V. Benzoic anhydride (0.679 g, 3.0 mmol) was used as the acylating species to which 1-adamantylamine (0.499 g, 3.3 mmol) was added. The compound was purified to give white crystals in a 0.623 g (81%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.65 (6H, br s, alkyl), 2.06 (9H, br s, alkyl), 5.74 (1H, br s, C(O)N<u>H</u>-), 7.29-7.43 (3H, m, aromatic), 7.64 (2H, d, J = 6.6 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 29.51, 36.40, 41.69, 52.29, 126.72, 128.47, 131.05, 136.05, 166.65. ESI -MS of $[C_{17}H_{21}NO]^+$; theoretical m/z of $[M+H]^+$ = 256.170, measured m/z of $[M+H]^+$ = 256.170, IR: υ = 1633.55 (C=O stretch). Consistent with the literature data.**[111]**

2.16 *N*-Phenyl benzamide:



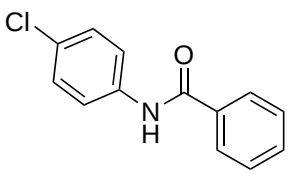
The title compound was formed following representative procedure V. Benzoic anhydride (0.679 g, 3.0 mmol) was used as the acylating species to which aniline (0.301 g, 3.3 mmol) was added. The compound was purified to give a faintly yellow powder in a 0.520 g (88%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.08 (1H, tt, J = 1.2 Hz, J = 7.2 Hz, aromatic), 7.29 (2H, tt, J = 1.8 Hz, J = 8.4 Hz, aromatic), 7.37-7.59 (5H, m, aromatic), 7.79 (2H, d, J = 7.8 Hz, aromatic), 7.84 (1H, br s, C(O)N<u>H</u>-R). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 120.24, 124.60, 127.05, 128.81, 129.13, 131.87, 135.01, 137.94, 165.82. ESI -MS of $[C_{13}H_{11}NO]^+$; theoretical m/z of $[M+H]^+$ = 198.092, measured m/z of $[M+H]^+$ = 198.092, IR: υ = 1652.93 (C=O stretch). Consistent with the literature data.**[33]**

2.17 *N*-4-Methylphenyl benzamide:



The title compound was formed following representative procedure V. Benzoic anhydride (0.679 g, 3.0 mmol) was used as the acylating species to which 4-toluidine (0.354 g, 3.3 mmol) was added. The compound was purified to give a white powder in a 0.510 g (81%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.34 (3H, s, CH_3-Ph), 7.16 (2H, d, J = 8.1 Hz, aromatic), 7.44-7.56 (5H, m, aromatic), 7.86 (2H, d, J = 6.9 Hz, aromatic), 7.86 (1H, br s, C(O)N<u>H</u>-R). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 20.95, 120.31, 127.03, 128.77, 129.60, 131.76, 134.26, 135.09, 135.38, 165.70. ESI -MS of $[C_{14}H_{13}NO]^+$; theoretical m/z of $[M+H]^+$ = 212.108, measured m/z of $[M+H]^+$ = 212.107, IR: υ = 1644.75 (C=O stretch). Consistent with the literature data.**[161]**

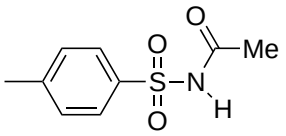
2.18 *N*-4-Chlorophenyl benzamide:



The title compound was formed following representative procedure V. Benzoic anhydride (0.679 g, 3.0 mmol) was used as the acylating species to which 4-chloroaniline

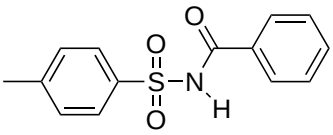
(0.421 g, 3.3 mmol) was added. The compound was purified to give a mauve powder in a 0.559 g (80%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.33 (2H, dt, J = 2.1 Hz, J = 8.7 Hz, aromatic), 7.47-7.63 (5H, m, aromatic), 7.81 (1H, br s, C(O)N<u>H</u>-R), 7.86 (2H, dt, J = 1.5 Hz, J = 6.9 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 121.40, 127.01, 128.91, 129.16, 132.10, 162.28. ESI -MS of $[C_{13}H_{10}NOCl]^+$; theoretical m/z of $[M+H]^+$ = 254.035, measured m/z of $[M+H]^+$ = 254.034, IR: υ = 1653.85 (C=O stretch). Consistent with the literature data.**[161]**

2.19 *N*-Acetyl-4-methylbenzenesulfonamide:



The title compound was formed following representative procedure VI. Acetic anhydride (0.284 mL, 3.0 mmol) was used as the acylating species to which *para*- toluenesulfonamide (0.565 g, 3.3 mmol) was added. The compound was purified to give a white powder in a 0.532 g (83%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.06 (3H, s, C<u>H</u>$_3$-C(O)-NH), 2.44 (3H, s, C<u>H</u>$_3$-Ph), 7.35 (2H, d, J = 8.1 Hz, aromatic), 7.93 (2H, d, J = 8.4 Hz, aromatic), 8.44 (1H, br s, C(O)-N<u>H</u>-). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 21.74, 23.53, 128.37, 129.73, 135.60, 145.34, 167.44. ESI -MS of $[C_9H_{11}NO_3S]^+$; theoretical m/z of $[M+H]^+$ = 214.054, measured m/z of $[M+H]^+$ = 214.052, IR: υ =1717.64 (C=O stretch). Consistent with the literature data.**[119]**

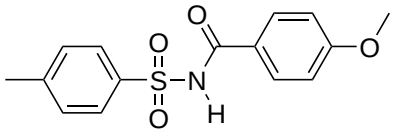
2.20 *N*-Benzoyl-4-methylbenzenesulfonamide:



The title compound was formed following representative procedure VI. Benzoic anhydride (0.679 g, 3.0 mmol) was used as the acylating species to which *para*- toluenesulfonamide (0.565 g, 3.3 mmol) was added. The compound was purified to give a white powder in a 0.454 g (55%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.44 (3H, s, C<u>H</u>$_3$-Ph), 7.35 (2H, d, J = 8.1 Hz, aromatic), 7.44 (2H, t, J = 7.8 Hz, aromatic), 7.57 (1H, t, J = 8.7 Hz, aromatic), 7.79 (2H, d, J = 8.4, aromatic), 8.04 (2H, d, J = 8.4 Hz, aromatic), 9.03 (1H, br s, C(O)N<u>H</u>). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 21.76, 127.87, 128.71,

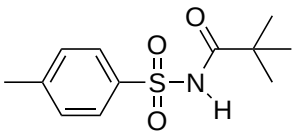
128.97, 129.67, 131.15, 133.54, 135.39, 146.33, 164.24. ESI -MS of $[C_{14}\,H_{13}NO_3S]^+$; theoretical m/z of $[M+H]^+$ = 276.069, measured m/z of $[M+H]^+$ = 276.069, IR: υ = 1700.38 (C=O stretch). Consistent with the literature data.**[124]**

2.21 *N*-4-Methoxybenzoyl-4-methylbenzenesulfonamide:



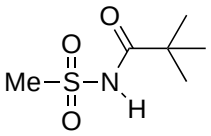
The title compound was formed following representative procedure VI. 4- Methoxybenzoic anhydride (0.287 g, 1.0 mmol) was used as the acylating species to which *para*-toluenesulfonamide (0.188 g, 1.1 mmol) was added. The compound was purified to give a white powder in a 0.198 g (69%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.44 (3H, s, C$\underline{H}_3$-Ph), 3.84 (3H, s, C$\underline{H}_3$-O-Ph), 6.91, 2H, d, J = 9.0 Hz, aromatic), 7.35, 2H, d, J = 8.1 Hz, aromatic), 7.75 (2H, d, J = 9.0 Hz, aromatic), 8.04 (2H, d, J = 8.4 Hz, aromatic), 8.80 (1H, br s, C(O)-N$\underline{H}$). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 21.75, 55.58, 114.21, 123.28, 128.69, 129.62, 129.91, 135.60, 145.15, 163.80. ESI -MS of $[C_{15}\,H_{15}NO_4S]^+$; theoretical m/z of $[M+H]^+$ = 306.080, measured m/z of $[M+H]^+$ = 306.080, IR: υ = 1666.67 (C=O stretch). Consistent with the literature data.**[124]**

2.22 *N*-Trimethylacetyl-4-methylbenzenesulfonamide:



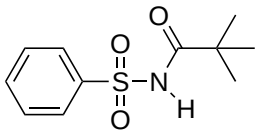
The title compound was formed following representative procedure VI. Pivalic anhydride (0.670 mL, 3.3 mmol) was used as the acylating species to which *para*- toluenesulfonamide (0.514 g, 3.0 mmol) was added. The compound was purified to give a white powder in a 0.766 g (83%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.08 (9H, s, ($C\underline{H}_3$)$_3$CC(O)), 2.38 (3H, s, C$\underline{H}_3$-Ph), 7.27 (2H, d, J = 8.1 Hz, aromatic), 8.88 (2H, dd, J = 8.4 Hz, aromatic), 8.34 (1H, br s, C(O)N$\underline{H}$-). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 21.74, 26.74, 39.98, 128.45, 129.62, 135.38, 145.08, 175.88. ESI -MS of $[C_{12}H_{17}NO_3S]^+$; theoretical m/z of $[M+H]^+$ = 256.100, measured m/z of $[M+H]^+$ = 256.099, IR: υ = 1709.33 (C=O stretch). Consistent with the literature data.**[124]**

2.23 *N*-Trimethylacetyl methanesulfonamide:



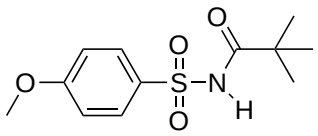
The title compound was formed following representative procedure VII. Pivalic anhydride (0.670 mL, 3.3 mmol) was used as the acylating species to which methane sulfonamide (0.285 g, 3.0 mmol) was added. The compound was purified to give a white powder in a 0.537 g (73%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.25 (9H, s, (C<u>H</u>$_3$)$_3$CC(O)), 3.31 (3H, s, C<u>H</u>$_3$-SO_2-), 8.16 (1H, br s, C(O)N<u>H</u>-). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 26.84, 40.07, 41.46, 177.25. ESI -MS of $[C_6H_{13}NO_3S]^+$; theoretical m/z of $[M+H]^+$ = 202.051, measured m/z of $[M+H]^+$ = 202.053, IR: υ = 1705.94 (C=O stretch). Consistent with the literature data.**[120]**

2.24 *N*-Trimethylacetyl benzenesulfonamide:



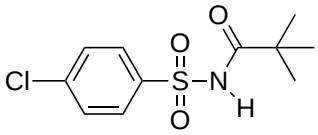
The title compound was formed following representative procedure VI. Pivalic anhydride (0.670 mL, 3.3 mmol) was used as the acylating species to which benzenesulfonamide (0.471 g, 3.0 mmol) was added. The compound was purified to give a white powder in a 0.724 g (85%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.08 (9H, s, (C<u>H</u>$_3$)$_3$CC(O)), 7.46-7.62 (3H, m, aromatic), 8.01 (2H, dd, J = 1.5 Hz, J = 7.2 Hz, aromatic), 8.46 (1H, br s, C(O)N<u>H</u>-). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 26.70, 40.03, 128.37, 129.00, 133.99, 138.37, 175.97. ESI -MS of $[C_{11}H_{15}NO_3S]^+$; theoretical m/z of $[M+H]^+$ = 242.085, measured m/z of $[M+H]^+$ = 242.085, IR: υ = 1704.15 (C=O stretch). Consistent with the literature data.**[119]**

2.25 *N*-Trimethylacetyl-4-methoxybenzenesulfonamide:



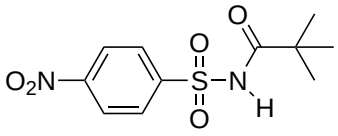
The title compound was formed following representative procedure VI. Pivalic anhydride (0.670 mL, 3.3 mmol) was used as the acylating species to which 4-methoxy benzenesulfonamide (0.562 g, 3.0 mmol) was added. The compound was purified to give a yellow powder with a 0.814 g (78%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.08 (9H, s, (C$\underline{H}_3$)$_3$CC(O)), 3.82 (3H, s, C$\underline{H}_3$-O-Ph), 6.93 (2H, d, J = 9.0 Hz, aromatic), 7.93 (2H, d, J = 9.0 Hz, aromatic), 8.24 (1H, br s, C(O)N$\underline{H}$-). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 26.78, 39.95, 55.71, 114.13, 129.67, 130.81, 163.90 . ESI -MS of $[C_{12}H_{17}NO_4S]^+$; theoretical m/z of $[M+H]^+$ = 294.078, measured m/z of $[M+H]^+$ = 294.075, IR: υ = 1713.85 (C=O stretch). Consistent with the literature data.**[124]**

2.26 *N*-Trimethylacetyl-4-chlorobenzenesulfonamide:



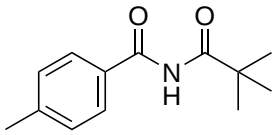
The title compound was formed following representative procedure VI. Pivalic anhydride (0.670 mL, 3.3 mmol) was used as the acylating species to which 4-chloro benzenesulfonamide (0.575 g, 3.0 mmol) was added. The compound was purified to give a white powder in a 0.827 g (83%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.09 (9H, s, (C$\underline{H}_3$)$_3$CC(O)), 7.46 (2H, d, J = 8.7 Hz, aromatic), 7.94 (2H, d, J = 8.7 Hz, aromatic), 8.20 (1H, br s, C(O)N$\underline{H}$-). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 26.71, 31.01, 40.04, 129.34, 129.94, 136.75, 140.73, 175.96. ESI -MS of $[C_{11}H_{14}NO_3SCl]^+$; theoretical m/z of $[M+H]^+$ =298.028, measured m/z of $[M+H]^+$ = 298.029, IR: υ = 1713.31 (C=O stretch).

2.27 *N*-Trimethylacetyl-4-nitrobenzenesulfonamide:



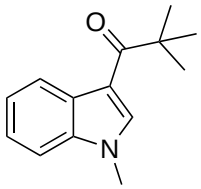
The title compound was formed following representative procedure VI. Pivalic anhydride (0.670 mL, 3.3 mmol) was used as the acylating species to which 4-nitro benzenesulfonamide (0.607 g, 3.0 mmol) was added. The compound was purified to give a white powder in 0.381 g (44%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.17 (9H, s, $(C\underline{H}_3)_3CC(O)$), 8.20 (1H, br s, C(O)N$\underline{H}$-), 8.27 (2H, d, J = 9.0 Hz, aromatic), 8.40 (2H, d, J = 9.0 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.17, 39.64, 123.66, 129.68, 143.83, 175.66. IR: υ = 171.38 (C=O stretch). Consistent with the literature data.**[124]**

2.28 *N*-Trimethylacetyl-4-toluimide:



The title compound was formed following representative procedure VIII. Pivalic anhydride (0.670 mL, 3.3 mmol) was used as the acylating species to which *p*-toluamide (0.405 g, 3.0 mmol) was added. The compound was purified by flash chromatography to give a white powder in a 0.238 g (36%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.24 (9H, s, $(C\underline{H}_3)_3$-C-C(O)-), 2.33 (3H, s, $C\underline{H}_3$-Ph), 7.18 (2H, d, J = 8.4 Hz, aromatic), 7.57 (2H, d, J = 8.4 Hz, aromatic), 8.54 (1H, br s, C(O)-N$\underline{H}$-C(O)). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 21.62, 27.16, 40.59, 127.78, 129.47, 131.00, 143.66, 166.17, 176.11. ESI -MS of $[C_{13}H_{17}NO_2]^+$; theoretical m/z of $[M+H]^+$ =220.134, measured m/z of $[M+H]^+$ = 220.133, IR: υ = 1723.15 (C=O stretch).

2.29 C_3-Trimethylacetyl-1-methylindole:



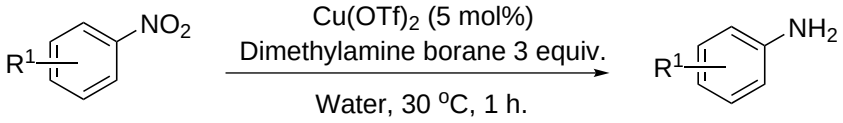
The title compound was formed following representative procedure IX. Pivalic anhydride (0.731 mL, 3.6 mmol) was used as the acylating species to which 1-methyl indole (0.374 ml, 3.0 mmol) was added. The compound was purified by recrystallisation from EtOAc to give yellow crystals in a 0.620 g (96%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ

= 1.34 (9H, s, (C<u>H</u>$_3$)$_3$-C-C(O)-), 3.76 (3H, s, C<u>H</u>$_3$-N), 7.18-7.23 (3H, m, aromatic), 7.71 (1H, s, C-C<u>H</u>-N), 8.43-8.46 (1H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 29.00, 33.52, 44.11, 109.26, 112.72, 122.51, 123.24, 123.41, 128.27, 134.39, 136.47, 202.23. ESI -MS of $[C_{14}H_{17}NO]^+$; theoretical m/z of $[M+H]^+$ =216.139, measured m/z of $[M+H]^+$ = 216.139, IR: υ = 1615.03 (C=O stretch). Consistent with the literature data.**[123]**

4.4 Experimental section for Chapter III

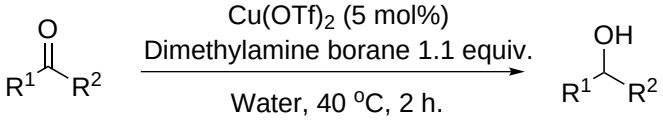
4.4.1 General procedures

4.4.1.1 General procedure for the reduction of aromatic nitro compounds; procedure (X)



To an oven dried Radleys tube was added copper(II) triflate (0.0543 g, 0.15 mmol) followed by deionised water (3 mL) then the substrate (3.0 mmol). Dimethylamine borane (0.530 g, 9 mmol) was added and the tube lids attached but not sealed. The reactions were heated at 30 °C for 1 h with stirring. After this time the reactions were briefly allowed to cool, diluted with DCM (25 mL) and separated from NaOH (10 mL, 2M) and brine (10 mL). The aqueous layer was washed two further times with DCM (10 mL) and the organic layers were collected, dried over $MgSO_4$, filtered and reduced *in vacuo* to give the product.

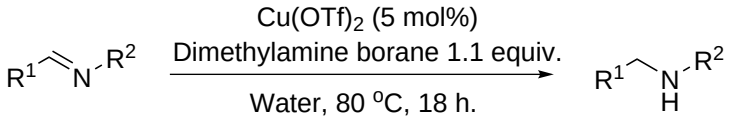
4.4.1.2 General procedure for the reduction of carbonyl compounds; procedure (XI)



To an oven dried Radleys tube was added copper(II) triflate (0.0543 g, 0.15 mmol) followed by deionised water (3 mL) then the substrate (3.0 mmol). Dimethylamine borane (0.0641 g, 1.1 mmol) was added and the tube lids attached but not sealed. The

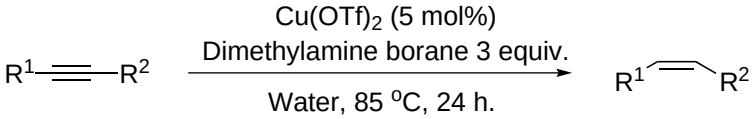
reactions were heated at 40 °C for 2 h with stirring. After this time the reactions were briefly allowed to cool, diluted with DCM (25 mL) and separated from brine (30 mL). The aqueous layer was washed two further times with DCM (10 mL) and the organic layers were collected, dried over $MgSO_4$, filtered and reduced *in vacuo* to give the product.

4.4.1.3 General procedure for the reduction of imine compounds; procedure (XII)



To an oven dried Radleys tube was added copper(II) triflate (0.0181 g, 0.05 mmol) followed by deionised water (1 mL) then the substrate (3.0 mmol). Dimethylamine borane (0.0641 g, 1.1 mmol) was added and the tube lids attached but not sealed. The reactions were heated at 80 °C for 18 h with stirring. After this time the reactions were briefly allowed to cool, diluted with DCM (25 mL) and separated from brine (30 mL). The aqueous layer was washed two further times with DCM (10 mL) and the organic layers were collected, dried over $MgSO_4$, filtered and reduced *in vacuo* to give the crude product. The product was dissolved in a minimal amount of ether and ethereal HCl (2M, 2mL) was added to form the salt which was precipitated out and collected by filtration after washing with Et_2O (20 mL).

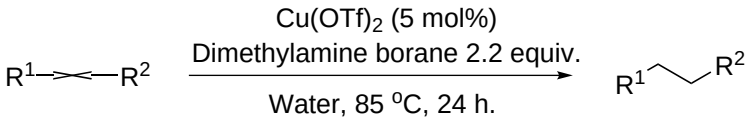
4.4.1.4 General procedure for the reduction of alkyne compounds; procedure (XIII)



To an oven dried Radleys tube was added copper(II) triflate (0.0543 g, 0.15 mmol) followed by deionised water (3 mL) then the substrate (3.0 mmol). Dimethylamine borane (0.1944 g, 3.3 mmol) was added and the tube lids attached but not sealed. The reactions were heated at 85 °C for 24 h with stirring. After this time the reactions were briefly allowed to cool, diluted with DCM (25 mL) and separated from brine (30 mL). The aqueous layer was washed two further times with DCM (10 mL) and the organic

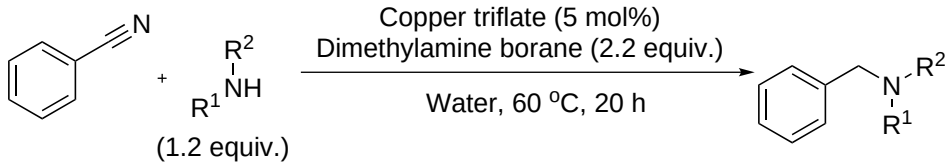
layers were collected, dried over $MgSO_4$, filtered and reduced *in vacuo* to give the crude product. The product was separated by column chromatography with hexanes through silica.

4.4.1.5 General procedure for the reduction of alkenes compounds; procedure (XIV)



To an oven dried Radleys tube was added copper(II) triflate (0.0543 g, 0.15 mmol) followed by deionised water (1.5 mL) then the substrate (3.0 mmol). Dimethylamine borane (0.3888 g, 6.6 mmol) was added and the tube lids attached but not sealed. The reactions were heated at 85 °C for 24 h with stirring. After this time the reactions were briefly allowed to cool, diluted with DCM (25 mL) and separated from brine (30 mL). The aqueous layer was washed two further times with DCM (10 mL) and the organic layers were collected, dried over $MgSO_4$, filtered and reduced *in vacuo* to give the crude product. The product was separated by column chromatography with hexanes through silica.

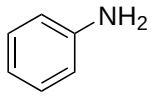
4.4.1.6 General procedure for the amination of nitriles; procedure (XV)



To an oven dried Radleys tube was added copper(II) triflate (0.543 g, 0.15 mmol) followed by deionised water (3 mL) then the amine (3.6 mmol). The solution was allowed to mix and then the nitrile specie was added (3.0 mmol). Dimethylamine borane (0.3889 g, 6.6 mmol) was added and the tube lids attached but not sealed. The reactions were heated at 60 °C for 20 h with stirring. After this time the reactions were briefly allowed to cool, diluted with DCM (25 mL) and separated from brine (30 mL). The aqueous layer was washed two further times with DCM (10mL) and the organic layers were collected, dried over $MgSO_4$, filtered and reduced *in vacuo* to give the crude product. Nitrile was separated from the product by means of a silica gel plug.

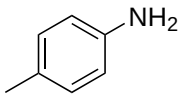
4.4.2 Products formed by reductions using a copper catalyst

3.1 Aniline:*



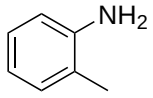
The title compound was formed following representative procedure X. 4-Nitrobenzene (0.308 mL, 3.0 mmol) was used as the substrate to which dimethylamine borane (0.530 g, 9.0 mmol) was added. The compound was purified by washing to give a yellow crystalline solid in a 0.242 g (86 %) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.69 (2H, br s, -N$\underline{H}_2$), 6.74 (2H, d, J = 8.7 Hz, aromatic), 6.86 (1H, t, J = 7.2 Hz, aromatic), 7.25 (2H, t, J = 8.1 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 115.24, 118.57, 129.42. ESI -MS of $[C_6H_7N]^+$; theoretical m/z of $[M+H]^+$ = 94.066, measured m/z of $[M+H]^+$ = 94.065. Consistent with the literature data supplied from a commercial source.

3.2 4-Aminotoluene:*



The title compound was formed following representative procedure X. 4-Nitrotoluene (0.411 g, 3.0 mmol) was used as the substrate to which dimethylamine borane (0.530 g, 9.0 mmol) was added. The compound was purified by washing to give a yellow crystalline solid in a 0.393 g (100%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.33 (3H, s, C$\underline{H}_3$-Ph), 3.64 (2H, br s, Ph-N$\underline{H}_2$), 6.66 (2H, d, J = 8.4 Hz, aromatic), 7.04 (2H, d, J = 8.4 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 20.59, 44.41, 115.47, 129.56, 144.06. ESI -MS of $[C_7H_9N]^+$; theoretical m/z of $[M+H]^+$ = 108.081, measured m/z of $[M+H]^+$ = 108.082. Consistent with the literature data supplied from a commercial source.

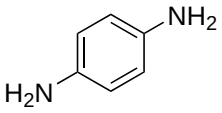
3.3 2-Aminotoluene:*



The title compound was formed following representative procedure X. 2-Nitrotoluene (0.354 mL, 3.0 mmol) was used as the substrate to which dimethylamine borane (0.530

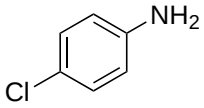
g, 9.0 mmol) was added. The compound was purified by washing to give a yellow liquid in a 0.276 g (86%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.20 (3H, s, C<u>H</u>$_3$-Ph), 3.49 (2H, br s, Ph-N<u>H</u>$_2$), 6.69-6.67 (2H, m, aromatic), 7.05-7.10 (2H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 17.43, 115.08, 118.46, 122.55, 126.72, 130.44, 144.58. ESI -MS of $[C_7H_9N]^+$; theoretical m/z of $[M+H]^+$ = 108.081, measured m/z of $[M+H]^+$ = 108.082. Consistent with the literature data supplied from a commercial source.

3.4 1,4-Diaminobenzene:*



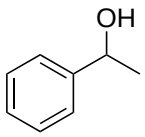
The title compound was formed following representative procedure X. 4-Nitroaniline (0.414 g, 3.0 mmol) was used as the substrate to which dimethylamine borane (0.530 g, 9.0 mmol) was added. The compound was purified by washing to give a dark red solid in a 0.113 g (34 %) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.35 (4H, br s, -N<u>H</u>$_2$), 6.57 (4H, s, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 116.55, 138.59. ESI -MS of $[C_6H_8N_2]^+$; theoretical m/z of $[M+H]^+$ = 109.076, measured m/z of $[M+H]^+$ = 109.077. Consistent with the literature data supplied from a commercial source.

3.5 4-Chloroaniline:*



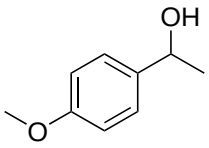
The title compound was formed following representative procedure X. 4-Chloro nitrotoluene (0.473 g, 3.0 mmol) was used as the substrate to which dimethylamine borane (0.530 g, 9.0 mmol) was added. The compound was purified by washing to give yellow crystals in a 0.358 g (94%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.50 (2H, br s, Ph-N<u>H</u>$_2$), 6.51 (2H, dt, J = 3.3 Hz, J = 8.7 Hz, aromatic), 7.01 (2H,dt, J = 3.3 Hz, J = 8.7 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 116.29, 122.97, 129.33, 144.63. ESI -MS of $[C_6H_6NCl]^+$; theoretical m/z of $[M+H]^+$ = 128.027, measured m/z of $[M+H]^+$ = 128.028. Consistent with the literature data supplied from a commercial source.

3.6 1-Phenyl ethanol:



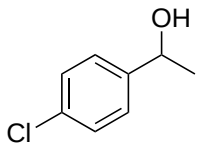
The title compound was formed following representative procedure XI. Acetophenone (0.350 mL, 3.0 mmol) was used as the substrate to which dimethylamine borane (0.064 g, 1.1 mmol) was added. The compound was purified by washing followed by column chromatography eluted by a mixture of ethyl acetate and pentane to give a colourless liquid in a 0.364 g (99%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.47 (3H, d, J = 6.6 Hz, C$\underline{H}_3$-CH-OH), 2.69 (1H, br s, CH-O$\underline{H}$), 4.83 (1H, q, J = 6.6 Hz, CH_3-C$\underline{H}$-OH), 7.23-7.39 (5H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 24.89, 70.19, 125.88, 127.44, 128.45, 145.39. ESI -MS of $[C_8H_{10}O]^+$; theoretical m/z of $[M\text{-}H_2O+H]^+$ = 105.070, measured m/z of $[M\text{-}H_2O+H]^+$ = 105.070. Consistent with the literature data.**[154]**

3.7 4'-Methoxy-1-phenylethanol:



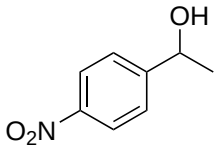
The title compound was formed following representative procedure XI. 4-Methoxy acetophenone (0.457 g, 3.0 mmol) was used as the substrate to which dimethylamine borane (0.064 g, 1.1 mmol) was added. The compound was purified by washing followed by column chromatography eluted by a mixture of ethyl acetate and pentane to give a yellow liquid in a 0.362 g (79%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.46 (3H, d, J = 7.5 Hz, C$\underline{H}_3$-CH-OH), 2.14 (1H, br s, CH-O$\underline{H}$), 3.79 (3H, s, C$\underline{H}_3$-O-Ph), 4.82 (1H, q, J = 6.6 Hz, CH_3-C$\underline{H}$-OH), 6.87 (2H, d, J = 8.4 Hz, aromatic), 7.28 (2H, d, J = 7.5 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 25.05, 55.30, 69.93, 113.82, 126.71, 138.06, 158.92. ESI -MS of $[C_9H_{12}O_2]^+$; theoretical m/z of $[M+H]^+$ = 175.074, measured m/z of $[M+H]^+$ = 175.073. Consistent with the literature data.**[162]**

3.8 4'-Chloro-1-phenylethanol:*



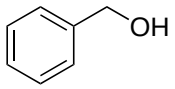
The title compound was formed following representative procedure XI. 4-Chloro acetophenone (0.389 mL, 3.0 mmol) was used as the substrate to which dimethylamine borane (0.064 g, 1.1 mmol) was added. The compound was purified by washing followed by column chromatography eluted by a mixture of ethyl acetate and pentane to give a clear liquid in a 0.469 g (99%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.42 (3H, d, J = 6.3 Hz, C<u>H</u>$_3$-CH-OH), 2.66 (1H, br s, CH-O<u>H</u>), 4.80 (1H, m, CH_3-C<u>H</u>-OH), 7.23-7.33 (4H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 25.24, 69.10, 126.73, 127.81, 133.09, 143, 84. ESI -MS of $[C_8H_9OCl]^+$; theoretical m/z of $[M\text{-}H_2O+H]^+$ = 139.031, measured m/z of $[M\text{-}H_2O+H]^+$ = 139.033. Consistent with the literature data supplied from a commercial source.

3.9 4'-Nitro-1-phenylethanol:



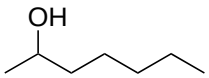
The title compound was formed following representative procedure XI. 4-Nitro acetophenone (0.496 g, 3.0 mmol) was used as the substrate to which dimethylamine borane (0.064 g, 1.1 mmol) was added. The compound was purified by washing followed by column chromatography eluted by a mixture of ethyl acetate and pentane to give a yellow solid in a 0.194 g (39%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.51 (3H, d, J = 6.6 Hz, C<u>H</u>$_3$-CH-OH), 2.07 (1H, br s, CH-O<u>H</u>), 5.01 (1H, q, J = 6.3 Hz, CH_3-C<u>H</u>-OH), 7.53 (2H, d, J = 9.0 Hz, aromatic) 8.18 (2H, d, J = 8.7 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 25.64, 69.77, 123.32, 125.94, 146.91, 152.84. ESI -MS of $[C_8H_9NO_3]^+$; theoretical m/z of $[M+H]^+$ = 190.048, measured m/z of $[M+H]^+$ = 190.047. Consistent with the literature data.**[162]**

3.10 Benzyl alcohol:*



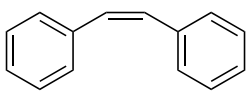
The title compound was formed following representative procedure XI. Benzaldehyde (0.306 mL, 3.0 mmol) was used as the substrate to which dimethylamine borane (0.064 g, 1.1 mmol) was added. The compound was purified by washing followed by column chromatography eluted by a mixture of ethyl acetate and pentane to give a pale yellow liquid in a 0.243 g (75%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.27 (1H, br s, CH_2-O<u>H</u>), 4.62 (2H, s, Ph-C<u>H</u>$_2$-OH), 7.26-7.39 (5H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 45.06, 65.28, 127.02, 128.52, 130.01, 140.89. ESI -MS of $[C_7H_8O]^+$; theoretical m/z of $[M\text{-}H_2O+H]^+$ = 91.054, measured m/z of $[M\text{-}H_2O+H]^+$ = 91.054. Consistent with the literature data supplied from a commercial source.

3.11 2-Heptanol:*



The title compound was formed following representative procedure XI. 2-Heptanone (0.418 mL, 3.0 mmol) was used as the substrate to which dimethylamine borane (0.064 g, 1.1 mmol) was added. The compound was purified by washing followed by column chromatography eluted by a mixture of ethyl acetate and pentane to give a yellow liquid in a 0.294 g (84%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.82 (3H, t, CH_2-CH_2-C<u>H</u>$_3$), 1.10 (3H, d, J = 6.0 Hz, C<u>H</u>$_3$-CH-OH), 1.17-1.45 (8H, m, aliphatic chain), 2.14 (1H, br s, CH-O<u>H</u>), 3.70 (1H, q, J = 5.1 Hz, CH_3-C<u>H</u>-OH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 13.69, 21.92, 23.35, 25.31, 31.68, 39.16, 67.97. ESI -MS of $[C_7H_{16}O]^+$; theoretical m/z of $[M\text{-}H_2O+H]^+$ = 99.117, measured m/z of $[M\text{-}H_2O+H]^+$ = 99.117. Consistent with the literature data supplied from a commercial source.

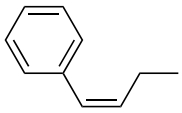
3.12 *Cis*-stilbene*



The title compound was formed following representative procedure XIII. Bis-phenyl acetylene (0.535 g, 3.0 mmol) was used as the substrate to which dimethylamine borane

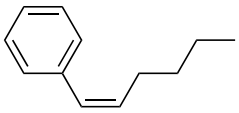
(0.389 g, 6.6 mmol) was added. The compound was purified by washing to give a clear liquid in a 0.523 g (97%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.72 (2H, t, J = 3.3 Hz, PhC<u>H</u>-CH-), 7.26-7.38 (10H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 127.27, 128.38, 129.04, 130.41, 137.39. IR: υ = 1600.05 (C=C stretch). Consistent with the literature data supplied from a commercial source.

3.13 1-Phenylbutene:



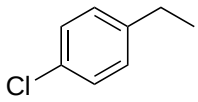
The title compound was formed following representative procedure XIII. 1-Phenyl butyne (0.426 mL, 3.0 mmol) was used as the substrate to which dimethylamine borane (0.389 g, 6.6 mmol) was added. The compound was purified by washing to give a yellow liquid in a 0.397 g (98%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.14 (3H, t, J = 7.5 Hz, C<u>H</u>$_3$-CH$_2$-CH-), 2.43 (2H, m, CH$_3$-C<u>H</u>$_2$-CH-) 5.66-5.77 (1H, m, CH$_2$-C<u>H</u>=CH-), 6.46 (1H, d, J = 13.0 Hz, CH=C<u>H</u>-Ph), 7.26-7.44 (5H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 14.46, 21.91, 125.94, 128.19, 128.83, 134.50, 137.89. IR: υ = 1601.23 (C=C stretch). Consistent with the literature data.[163]

3.14 1-Phenylhexene:



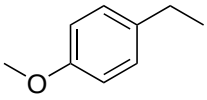
The title compound was formed following representative procedure XIII. 1-Phenyl hexyne (0.528 mL, 3.0 mmol) was used as the substrate to which dimethylamine borane (0.389 g, 6.6 mmol) was added. The compound was purified by washing to give a clear liquid in a 0.421 g (88%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.94 (3H, t, J = 6.0 Hz, C<u>H</u>$_3$-CH$_2$-CH$_2$-), 1.36-1.53 (4H, m, CH$_3$-C<u>H</u>$_2$-C<u>H</u>$_2$-), 2.37 (2H, q, J = 7.2 Hz, CH$_2$-CH$_2$-C<u>H</u>$_2$-CH-), 5.66-5.75 (1H, m, CH$_2$-C<u>H</u>=CH-), 6.45 (1H, d, J = 13.0 Hz, CH=C<u>H</u>-Ph), 7.21-7.39 (5H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 14.06, 22.70, 28.62, 32.35, 126.46, 128.15, 128.72, 128.81, 133.23137.87. IR: υ = 1600.22 (C=C stretch). Consistent with the literature data.[164]

3.15 4-Ethyl chlorobenzene:*



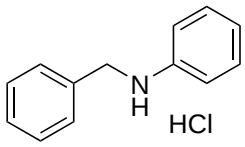
The title compound was formed following representative procedure XIV. 4-Chloro styrene (0.36 mL, 3.0 mmol) was used as the substrate to which dimethylamine borane (0.389 g, 6.6 mmol) was added. The product and remaining starting material were separated from the reaction mixture by washing to give a clear liquid in a 0.285 g yield of which 71% was determined to be the product by analysis of NMR spectroscopy. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.23 (3H, t, J = 7.5 Hz, $C\underline{H}_3$-CH_2-Ph), 2.62 (2H, q, J = 7.5 Hz, CH_3-$C\underline{H}_2$-Ph), 7.24-7.36 (4H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 15.59, 28.29, 127.28, 128.32, 129.25, 135.69. Consistent with the literature data supplied from a commercial source.

3.16 4-Ethyl methoxybenzene:*



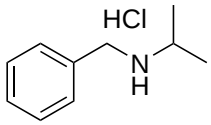
The title compound was formed following representative procedure XIV. 4-Methoxy styrene (0.399 mL, 3.0 mmol) was used as the substrate to which dimethylamine borane (0.389 g, 6.6 mmol) was added. The product and remaining starting material were separated from the reaction mixture by washing to give a mauve liquid in a 0.362 g yield of which 72% was determined to be the product by analysis of NMR spectroscopy. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.29 (3H, t, J = 7.8 Hz, $C\underline{H}_3$-CH_2-Ph), 2.65 (2H, q, J = 7.5 Hz, CH_3-$C\underline{H}_2$-Ph), 6.91 (2H, d, J = 8.4 Hz, aromatic), 7.19 (2H, d, J = *8.7* Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 15.22, 27.85, 55.16, 113.56, 128.57, 135.64, 157.71. Consistent with the literature data supplied from a commercial source.

3.17 *N*-Benzyl aniline hydrochloride:*



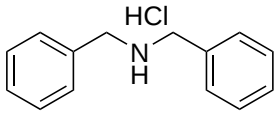
The title compound was formed following representative procedure XII. *N*-Benzylidine aniline (0.181 g, 1.0 mmol) was used as the substrate to which dimethylamine borane (0.064 g, 1.1 mmol) was added. The product and remaining starting material were separated from the reaction mixture by washing, dissolving in a minimal amount of ether and acidification with ethereal HCl to give a pale green precipitate. This was filtered, washed with ether and dried to give the product in a 0.182 g (83%) yield. ^{1}H NMR (300 MHz, DMSO) δ = 4.44 (2H, s, Ph-C$\underline{H}_2$-NH), 7.13-7.25 (3H, m, aromatic), 7.28-7.36 (5H, m, aromatic), 7.44-7.47 (2H, d, J = 7.8 Hz), 7.56 (1H, br s, N$\underline{H}$). ^{13}C NMR (75.5 MHz, DMSO) δ = 52.08, 120.97, 125.76, 128.64, 128.73, 129.76, 129.96, 134.18. ESI -MS of $[C_{13}H_{13}N]^+$; theoretical m/z of $[M+H]^+$ =184.113, measured m/z of $[M+H]^+$ = 184.113. Consistent with the literature data supplied from a commercial source.

3.18 *N*-Isopropyl benzylamine:



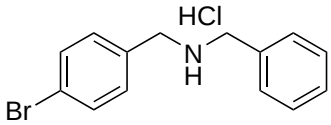
The title compound was formed following representative procedure XII. *N*-Benzylidine isopropylamine (0.441 g, 3.0 mmol) was used as the substrate to which dimethylamine borane (0.1923 g, 3.3 mmol) was added. The product and remaining starting material were separated from the reaction mixture by washing, dissolving in a minimal amount of ether and acidification with ethereal HCl to give a white precipitate. This was filtered, washed with ether and dried to give the product in a 0.343 g (70%) yield. ^{1}H NMR (300 MHz, DMSO) δ = 1.28 (6H, d, J = 6.3 Hz, C$\underline{H}_3$-CH), 3.23 (1H, br s, CH$_3$-C$\underline{H}$), 4.09 (2H, s, Ph-C$\underline{H}_2$), 7.35-7.45 (3H, m, aromatic), 7.55-7.59 (2H, m, aromatic), 9.19 (1H, br, s, N$\underline{H}$). ^{13}C NMR (75.5 MHz, DMSO) δ = 18.89, 47.46, 49.69, 128.98, 129.14, 130.33, 132.68. ESI -MS of $[C_{10}H_{16}N]^+$; theoretical m/z of $[M+H]^+$ = 151.136, measured m/z of $[M+H]^+$ = 151.133. Consistent with the literature data.**[162]**

3.19 Dibenzylamine hydrochloride:



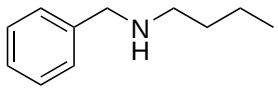
The title compound was formed following representative procedure XII. *N*-Benzylidine benzylamine (0.195 g, 1.0 mmol) was used as the substrate to which dimethylamine borane (0.064 g, 1.1 mmol) was added. The product and remaining starting material were separated from the reaction mixture by washing, dissolving in a minimal amount of ether and acidification with ethereal HCl to give a white precipitate. This was filtered, washed with ether and dried to give the product in a 0.151 g (65%) yield. ^{1}H NMR (300 MHz, DMSO) δ = 4.10 (4H, m, (N-C$\underline{H}_2$-Ph)$_2$), 7.34-7.62 (10H, m, aromatic), 9.88 (H, br s, N$\underline{H}$). ^{13}C NMR (75.5 MHz, DMSO) δ = 49.87, 122.66, 130.52, 131.81, 132.85. ESI -MS of $[C_{14}H_{15}N]^{+}$; theoretical m/z of $[M+H]^{+}$ =198.128, measured m/z of $[M+H]^{+}$ = 198.130. Consistent with the literature data.**[154]**

3.20 *N*-Benzyl-4-benzylamine:*



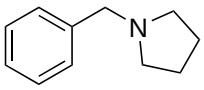
The title compound was formed following representative procedure XII. *N*-4-Bromo benzylidine benzylamine (0.274 g, 1.0 mmol) was used as the substrate to which dimethylamine borane (0.064 g, 1.1 mmol) was added. The product and remaining starting material were separated from the reaction mixture by washing, dissolving in a minimal amount of ether and acidification with ethereal HCl to give a white precipitate. This was filtered, washed with ether and dried to give the product in a 0.273 g (87%) yield. ^{1}H NMR (300 MHz, DMSO) δ = 4.55 (2H, s, Ph-C$\underline{H}_2$-N), 4.57 (2H, s, Ph-C$\underline{H}_2$-N), 6.52 (1H, br s, NH), 7.03 (2H, t, J = 8.7 Hz, aromatic), 7.24-7.33 (5H, m, aromatic), 7.71-7.77 (2H, m, aromatic). ^{13}C NMR (75.5 MHz, DMSO) δ = 49.27, 49.98, 122.64, 128.90, 129.20, 130.55, 131.38, 131.78, 132.25, 132.88. ESI -MS of $[C_{14}H_{14}NBr]^{+}$; theoretical m/z of $[M+H]^{+}$ =276.039, measured m/z of $[M+H]^{+}$ = 276.038. Consistent with the literature data supplied from a commercial source.

3.21 *N*-Benzylbutylamine:



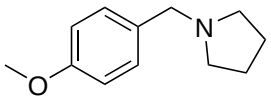
The title compound was formed following representative procedure XV. Butylamine (0.356 mL, 3.6 mmol) was used and the nucleophile and was added to benzonitrile (0.309 mL, 3.0 mmol). Dimethylamine borane (0.389 g, 6.6 mmol) was added and the reaction allowed to react for 20 h. Upon completion of the reaction the organic layer was extracted by DCM from water and the aqueous layer washed a further two times with DCM. After purification the product was isolated in a 0.230 g (47%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.92 (3H, t, J = 7.2 Hz, C$\underline{H}_3$-CH_2), 1.29-1.56 (4H, m, aliphatic), 1.77 (1H, br s, NH), 2.64 (2H, t, J = 7.2 Hz, NH-C$\underline{H}_2$), 3.80 (2H, s, Ph-C$\underline{H}_2$), 7.27-7.41 (5H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 14.07, 27.52, 32.18, 49.16, 54.06, 126.94, 128.20, 128.42, 140.36. ESI -MS of $[C_{11}H_{17}N]^+$; theoretical m/z of $[M+H]^+$ = 164.144, measured m/z of $[M+H]^+$ = 164.146.Consistent with the literature data.**[153]**

3.22 *N*-Benzylpyrrolidine:



The title compound was formed following representative procedure XV. Pyrrolidine (0.296 mL, 3.6 mmol) was used and the nucleophile and was added to benzonitrile (0.309 mL, 3.0 mmol). Dimethylamine borane (0.389 g, 6.6 mmol) was added and the reaction allowed to react for 20 h. Upon completion of the reaction the organic layer was extracted by DCM from water and the aqueous layer washed a further two times with DCM. After purification the product was isolated in a 0.400 g (72%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.80 (4H, m, C$\underline{H}_2$-CH_2-N), 2.53 (4H, m, CH_2-C$\underline{H}_2$-N), 3.63 (2H, s, Ph-C$\underline{H}_2$), 7.29-7.41 (5H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 23.44, 54.19, 60.70, 127.01, 128.27, 129.02, 139.22. ESI -MS of $[C_{11}H_{15}N]^+$; theoretical m/z of $[M+H]^+$ = 162.129, measured m/z of $[M+H]^+$ = 162.130. Consistent with the literature data.**[165]**

3.23 *N*-4-Methoxybenzylpyrrolidine:



The title compound was formed following a slight modification on representative procedure XV. Pyrrolidine (0.320 mL, 3.9 mmol) was used and the nucleophile and was added to benzonitrile (0.309 mL, 3.0 mmol). Dimethylamine borane (0.389 g, 6.6 mmol) was added and the reaction allowed to react at 45 °C for 20 h. Upon completion of the reaction the organic layer was extracted by DCM from water and the aqueous layer washed a further two times with DCM. After purification the product was isolated in a 0.461 g (80%) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.77 (4H, m, C$\underline{H}_2$-CH_2-N), 2.46 (4H, m, CH_2-C$\underline{H}_2$-N), 3.54 (2H, s, Ph-C$\underline{H}_2$), 3.78 (3H, s, C$\underline{H}_3$-O-Ph), 6.83 (2H, d, J = 8.7 Hz, aromatic), 7.24 (2H, d, J = 8.7 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 23.37, 54.02, 55.24, 60.10, 113.55, 130.03, 131.54, 158.11. ESI -MS of $[C_{12}H_{17}NO]^+$; theoretical m/z of $[M+H]^+$ = 192.139, measured m/z of $[M+H]^+$ = 192.138. Consistent with the literature data.**[165]**

Chapter 5

Conclusions

5.1 Aminolysis of Esters

Previous methods for the aminolysis of esters have been reported with the majority of these requiring harsh reaction conditions or reagents. Alternative methods focus on the use of stoichiometric promoters such as metal amides or the use of stoichiometric additives in co-ordination with a catalyst such as a group(IV) alkoxide. These methods are not atom efficient and so finding an alternative, catalytic route that utilises an inexpensive catalyst in low catalytic loadings was desirable.

Previous group work focussing on transamidation reactions had shown the potential of thiocyanate additives to expedite reactions when used in conjunction with a zirconocene dichloride catalyst with the additive potentially activating the incoming amine. Optimisation showed that a range of Lewis acids could be used to promote the reaction of benzylamine with ethyl hydrocinnamate; in particular hard metal centres, especially zirconium, showed much increased conversions compared to the background rate. The addition of a range of thiocyanate additives was investigated with a significant enhancement in the conversions only being seen with the zirconocene dichloride catalyst.

Analogous catalysts to zirconocene dichloride were investigated and although hafnocene dichloride did show a greater level of reactivity the enhancement was not considerable enough to merit the increased price of the catalyst. Many of the thiocyanates showed good improvements to the catalytic rate with oven-dried ammonium thiocyanate proving the most effective additive. Anhydrous aliphatic solvents proved the best for the reaction with cyclohexane seeming to be the best although heptane was also good, particularly for reactions run above the boiling point of cyclohexane. Whilst the presence of air was not as detrimental to the reaction as the use of wet solvents, it was found

that purging the reactions with argon gave the best results.

The methodology discovered was proven to be applicable to a wide selection of aliphatic and aromatic esters as well as lactones. Similarly both anilinic, as well as primary and secondary aliphatic amines could be used as the incoming nucleophile to produce the desired amides in good to excellent yields. Importantly the methodology could be used for the formylation of amines which is useful as there are not many facile and safe synthons to replace the ester moiety. The limitations of the methodology showed that it was not an ideal system for the aminolysis of carboxylic acids, this can be attributed to the water molecules produced in the process interacting with the catalyst. The use of less nucleophilic analogues for amines such as sulfonamides also proved to be incompatible with the reaction, presumably due to their lower nucleophilicity.

Some mechanistic aspects of the reaction were investigated and NMR studies were used to determine that the thiocyanate additive is not acting as an acyl transfer reagent. It is thought instead that the thiocyanate salt is reacting with the zirconocene dichloride to form a different catalytic species, believed to be formed by salt metathesis with the chloride ligands. This species, formed *in situ*, is believed to be a much more potent catalyst under the reaction conditions as alternative NMR studies suggest it only forms in relatively small quantities in the brief time it is allowed to react before the reagents are added.

The methodology describes a inexpensive and efficient route for the under explored area of ester aminolysis using a non-harmful and relatively abundant metal catalyst. The reaction was seen to be robust and tolerant to a range of functional groups. Although ammonium thiocyanate proved to be the best additive investigated, many of the other thiocyanate salts also proved applicable with the formation of biologically important functionalities, such as heterocycles and the retention of enantiomeric purity, proving successful.

5.2 Anhydride Activation

Whilst much work has been conducted investigating the use of acid halides as acylating agents for a range of nucleophiles by various methods, acid anhydrides by comparison remain a comparatively understudied acyl source. A lot of literature surrounding acid anhydride activation focusses on the use of expensive metal triflates for the Lewis acid

activation of anhydrides to increase their electrophilicity or the use of alternative catalysts such as organocatalysts or molecular iodide, the latter which showed the ability to acylate with an anhydride surrogate; vinyl acetate.

The initial group interest in the subject derives from investigations looking into the optimum additive for the activation of DBN as an organic catalyst for acyl transfer. It was found that the addition of stoichiometric quantities of lithium iodide markedly increased the reactivity of the acyl group even when the DBN was not present. This was determined, primarily by the use of NMR techniques, to be proceeding through the formation of an acid iodide intermediate, vastly increasing the electrophilicity of the carbon of the acyl group. Further work expanded this methodology to provide a catalytic system using potassium iodide (60 mol%) for the acylation of a range of challenging and interesting nucleophiles. A continuation of the mechanistic studies showed an improvement in the reaction rate when the Lewis acid metal centre was present, compared to when it had been removed by the addition of a crown ether. This was less significant than the identity of the anion counterpart leading to the suggestion that the poor overlap of the iodide's electrons with the π^* of the carbonyl led to the significant enhancement in reactivity.

Investigating the use of s-block metal iodides in the activation of acid anhydrides showed that, of those looked at, magnesium iodide was the most efficient at catalysing the chosen reaction of acylating benzyl alcohol with benzoic anhydride. Polar solvents improved the reactivity with acetonitrile and dioxane both proving effective. Initially a wide range of alcohols was investigated for their acylation using various anhydrides, with high levels of success seen with low background rates recorded. Aliphatic and aromatic alcohols, as well as anhydrides, proved suitable for the methodology; tolerance was noted for heterocycles, halogens as well as quite considerable steric bulk around the substrate. Further work focussed on nitrogen nucleophiles with simple amine nucleophiles and anilinic species proving acylatable.

Sulfonamides are known to be considerable less nucleophilic than amines and so required longer reaction times and increased reaction temperatures. The use of the methodology to acylate *para*-toluene sulfonamide with a range of acid anhydrides was noted along with the use of pivalic anhydride, a sterically hindered, electron-rich anhydride as the acylating agent for a range of aliphatic and aromatic sulfonamides. Investigations into the acylation of more challenging nucleophiles showed that when small simple anhydrides were used, even very sterically encumbered and electron poor nucleophiles such as BHT could be acylated; the use of more demanding anhydrides such as pivalic

anhydride however stopped the reaction. Alternatively the use of very poor nucleophiles showed only low conversions even after extended times under harsh reaction conditions. Heterocycle acylations were investigated and the pivoylation of *N*-methyl indole was demonstrated in excellent yields although the use of alternative anhydrides led to a decomposition of the substrate upon isolation.

The mechanism of the reaction was investigated and NMR studies were used to show that the magnesium iodide did not form an acid iodide *in situ* as the corresponding acid chloride work within the group had shown. Instead the mechanism was believed to be proceeding through a Lewis acid activation pathway, this hypothesis was supported by the addition of a crown ether which successfully sequestered the magnesium ion and shut down the reaction.

5.3 Amine Borane Reductions and Reductive Coupling

Amine boranes are well studied substrates in the field of hydrogen release by the process of dehydrocoupling. The majority of the work within the literature focusses on predominantly heterogeneous methods for the release of molecular hydrogen for energy applications although some homogeneous methodologies have also been reported. The noble metals feature heavily in both arenas although more recent work has began to investigate the use of more sustainable and inexpensive metal catalysts such as nickel and chromium centred ones. Photo-catalysis has been investigated as a mechanism by which to activate catalysts towards dehydrogenation; in general this method has been for the removal of ligated ligands to produce an active site on the catalyst. Alternative methods of catalyst activation have been the formation of nano-particles or colloidal suspensions which have shown high catalytic activity and resulted in the rapid production of molecular hydrogen.

Considering the large amount of literature surrounding the dehydrogenation of amine boranes, there has been very few reports of their use in synthetic methodologies. Most of the reports using amine boranes in organic synthesis have again relied on the use of expensive noble group metals, occasionally in coordination with complex or sensitive ligand systems. Previous work within our own group has looked at the use of ruthenium based catalysts to reduce a range of organic functional groups such as; imines, nitriles, carbonyls and others using inexpensive, commercially available amine boranes.

Investigations were conducted with the intention of developing a robust methodology

for the amination of nitriles with either simple amines or ideally with anilines produced from the reduction of nitro-aromatics. Having had previous group success, both with the use of amine borane-ruthenium catalysed reductions as well as a range of ruthenium catalysed hydrogen transfer reductions, investigations along these themes were made. Initial success with a $[(p\text{-cymene})RuCl_2]_2$ catalyst showed some coupling between reduced 4-nitrotoluene species and some aliphatic and aromatic nitriles. The selectivities of these reactions were poor however with considerable levels of homo-coupling being seen from reduction of the nitrile to the nucleophilic amine. In an attempt to increase the selectivities; co-catalysts were used with copper acetate proving to significantly increase the rate of reduction of the organic groups.

It was determined that the copper could act as a reductive catalyst on its own as opposed to solely as a co-catalyst for the ruthenium with highly efficient reductions of nitro-aromatics in particular. Optimisation of the methodology showed that a wide range of copper salts and oxides could be used with both copper triflate and copper sulfate proving particularly effective. Water was a good solvent for the reactions which is particularly beneficial when considering its green credentials.

A wide range of functionalities showed good to excellent reductions under the optimised reaction conditions with; imines, carbonyls, primary styrene-alkenes and a selection of aromatic nitro compounds showing good reduction. Under certain reaction conditions alkynes could be selectively reduced to yield the alkenes in high conversions with little over reduction to the alkene seen by ^{1}H NMR. The reduction of aliphatic nitro compounds was less successful with a large quantity of side product seen instead.

Attempts to aminate nitriles showed mixed success with anilines produced by the reduction of nitro-aryls proving too poorly nucleophilic to show much selectivity. The use of highly nucleophilic amines such as butylamine or pyrrolidine however did show some good conversions to the desired secondary and tertiary amines respectively. Investigations into the robustness of the methodology with respect to the nature of the nitrile species showed that aromatic nitriles were far more favourable for amination by an incoming nucleophile than the aliphatic counterparts. Even for aromatic nitriles the electronic and steric configuration of the electrophile appears to play a significant role in determining the selectivity between heterogeneously aminated product and the homo-coupled product of nitrile reduction.

The mechanism by which the reductions were occurring was investigated by a combination of experimental and spectroscopic techniques. Kinetic ^{1}H NMR data sets were

taken and these showed the presence of an induction period prior to rapid formation of the anilinic species from the starting 4-nitrotoluene. This suggests a heterogeneous catalytic mechanism either through a delay required for the formation of metal particulates from their starting precursor or an auto-catalytic methodology. A second piece of data, the addition of elemental mercury, reduced the rate of the reaction to the equivalent reached when no catalyst had been added. This suggests that the catalyst is in a heterogeneous phase and either being poisoned by the mercury or forming an amalgam with it resulting in the lack of catalytic activity seen.

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